

BULLETIN

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MAHLON ASHFORD, *Editor*

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JANUARY 1947

CENTENNIAL CELEBRATION

1847 — 1947

THE year 1947 marks the completion of the first hundred years of The New York Academy of Medicine. As is fitting and proper, the Council and Trustees of the Academy have decided to devote the months of March and April 1947 to a celebration of this Centenary.

The dominant thought which will motivate the program of this Celebration will be, not so much the recital of the Academy's fascinatingly interesting history, as an evaluation of its accomplishments in terms of present day thought and its implications for the future of medicine and the community at large. For a century, the Academy has served the medical profession—practicing, teaching, and fostering research in matters of medical education, public health and public relations. From these roots have grown its work for the public weal, particularly in public health and welfare. The Academy has become a valued portion of the warp and woof of our whole community fabric. This foundation of a hundred years is important only in so far as it serves as a basis for future intellectual and spiritual growth; only in so far as it prepares the Academy to meet new problems and to explore new fields.

This Centennial Celebration will open with a Dinner on March 6.

1947 at the Waldorf-Astoria Hotel, to which the Fellows, their wives and friends of the Academy will be invited.

Subsequent to the Dinner, extending over the span of two months, each of the eleven Sections of the Academy will present programs in keeping with the spirit of the Centenary. These programs are under the charge of the Section Chairmen. It is the hope of the Centennial Committee that through these media, the entire Fellowship of the Academy may participate actively in this Centennial Celebration.

In addition to the Section meetings, there will be four conferences or Institutes—one on Public Health; another on the problems of Medical Education; a third devoted to what is termed Social Medicine, a discussion of the influence of modern medicine on the larger social groups, as well as conversely, the implications of the impact of changing social orders on medicine itself. The fourth Institute will consider the problems of specialized libraries, particularly medical and scientific libraries. These Institutes will occupy periods of two to three days each.

Societies and organizations affiliated with the Academy either in fact, or through association of interests and aims, will coöperate in the Centenary.

Two publications will appear in 1947 under the auspices of the Academy, which will be of major interest. The Report of the Committee on Medicine and the Changing Order will be published by the Commonwealth Fund prior to the initiation of the Centennial Celebration. This work represents the results of a three and a half year study on the part of a large Committee of Fellows of the Academy and laymen. Later in the year, there will appear a History of the Academy over its first century. This volume has been in the process of preparation for about two years and promises to be a major contribution, not only to the history of medicine in New York, but as well a contribution to the history of the City itself.

Inherent in the aims of these plans is the thought of having as broad a participation as possible by the entire Fellowship of the Academy in the Centennial Celebration. Details of programs and dates of various exercises will appear in the Academy Bulletin, and in addition, will be sent to each Fellow individually.

TUMORS OF THE THYROID *

SHIELDS WARREN

Pathologist, New England Deaconess Hospital, Boston

THYROID tumors have been of constant interest because of the difficulty of diagnosis of certain types; now the possibility has been raised that radioactive iodine may offer a useful therapeutic tool.

Most enlargements of the thyroid are not tumors. Enlargement of the gland, either diffuse or nodular, is much more frequently due to metabolic disorders than to neoplasia. Until recent years, there has been much confusion between the true adenomas of the thyroid and the nodular hyperplasias, and still some room for argument exists.

I have found the following criteria for adenoma of the thyroid to be helpful in differentiating this lesion from thyroid nodules of non-neoplastic origin. First, an adenoma should represent a single homogeneous type of tissue. Second, it should be definitely encapsulated. Third, it should compress surrounding thyroid tissue. Usually, it differs sharply in histology from the surrounding tissue. In some of the nodular goiters, even these criteria may prove unsatisfactory and uncertainty may exist as to type of lesion with which we are dealing.

The origin of thyroid adenomas is as uncertain as the origin of adenomas in other organs. In our laboratory five types of adenoma are recognized: the embryonal adenoma, in which masses and strands of poorly differentiated thyroid cells traverse a rather gelatinous stroma; the fetal adenoma, in which poorly developed follicles occur, usually embedded in a rather abundant gelatinous stroma; the simple adenoma which may closely resemble the histologic picture of the normal thyroid gland; the colloid adenoma, in which extensive storage of colloid occurs, and the follicles are greatly distended; the Hürthle cell type of adenoma, characterized by large polyhedral cells with rather strikingly clear cytoplasm.

* Read at The New York Academy of Medicine at the 19th Graduate Fortnight, October 8, 1946.

The so-called toxic adenoma is quite frequently diagnosed but very rarely occurs. Usually, when this term is applied, it is used to describe a nodular goiter with associated hyperthyroidism. Hyperfunction of the cells of an adenoma is one of the rarest changes encountered.

The adenomas are also of special interest because of the borderline position which they occupy between the benign tumors on the one hand and the malignant tumors on the other. There is a group of thyroid adenomas, usually indistinguishable from other adenomas grossly, which give rise to metastasis. The metastases may faithfully reproduce the parent adenoma or they may be even more differentiated resembling well-formed adult thyroid tissue, the so-called benign metastasizing goiter. The only clue to the malignancy of these tumors may be invasion of one or more veins by the neoplastic tissue. Sometimes this is grossly obvious with a solid cord of tumor filling one of the major thyroid veins or even the jugular vein. More often it is relatively inconspicuous and only microscopic examination will reveal its presence. This vascular invasion may or may not be accompanied by some invasion of the capsule. Not every case that shows microscopic evidence of blood vessel invasion develops metastases. Indeed, the frequency is under 10 per cent. It is likely that a relatively extensive amount of vascular invasion occurs before metastases become established, since the proportion of tissue removed for histologic examination is relatively small. Interestingly enough, I have seen only one case in which we did not find blood vessel invasion and in which metastases subsequently developed.

As would be expected from the high degree of differentiation of these tumors, their clinical course is relatively slow. Metastases occur most frequently in bone. In one case I recall, the patient lived seven years after the metastases were discovered. Likewise, a long latent period may pass between the development of the primary tumor and the appearance of metastases.

The commonest of the adenomas to show blood vessel invasion, as would be expected from their growth potentialities, are the embryonal and the fetal adenomas. In checking for the occurrence of blood vessel invasion, it is important not to be misled by artefacts. In the course of preparation of the sections, it is quite possible that portions of the tumor may be dislodged and caught in the blood vascular spaces. Consequently, I always like to see actual invasion of the wall of the vessel by the

tumor or adherence of the tumor tissue to the wall.

As was so clearly pointed out by Graham, the propensity to invade blood vessels is quite striking in all types of thyroid malignant tumors, regardless of their degree of differentiation, and is consequently a very valuable criterion of malignancy.

There has been a good deal of controversy concerning the papilliferous tumors. These may arise from the thyroid proper or from lateral aberrant thyroid tissue. The five types described by Moritz and Bayless are useful in considering this group: (1) The papilliferous cystadenoma, a benign tumor which represents hyperplasia of the lining epithelium of a cystic adenoma; (2) the papilliferous adenoma, which represents epithelial proliferation of an hyperplastic type within the follicles of a pre-existing adenoma, and is non-malignant; (3) the papilliferous carcinoid, which represents focal papillary hyperplasia, is non-encapsulated and occurs in a non-neoplastic thyroid gland; (4) the papilliferous adenocarcinoma arising from malignant change in a papilliferous cystadenoma, which shows capsular invasion or metastasis to regional lymph nodes; and (5) the papilliferous malignant adenoma, which shows a papillary intra-acinar hyperplasia in an adenoma with malignant characteristics, i.e., blood vessel invasion, capsular invasion, and sometimes metastasis to regional lymph nodes.

It has been our custom to differentiate three types of true papillary tumors: The benign papillary cystadenomas which may originate either within the thyroid or in lateral aberrant thyroid tissue, which are not clinically dangerous; the malignant papillary adenocystomas which seem to have the same origin as the foregoing but which, because of a greater growth potential, may metastasize chiefly to regional lymph nodes or lungs, invade blood vessels, and invade local tissues; the papillary adenocarcinoma which will be mentioned further later.

Even in those papillary cystadenomas that are malignant, the clinical course tends to be relatively slow, and fortunately, the results obtained with surgery combined with roentgen radiation are fairly satisfactory. Two-thirds of all patients treated were surviving at the end of five years.

When one finds a papillary tumor of thyroid origin in the neck, the problem always arises as to whether or not the thyroid should be removed either wholly or in part. If the thyroid is normal on palpation, there is no reason for operative interference, and it may safely be assumed that the tumor is of lateral aberrant origin. If, however, there is

enlargement or irregularity of the thyroid, at least a hemi-thyroidectomy including the abnormal tissue is indicated.

In the group of thyroid tumors of moderate malignancy we include the adenocarcinomas. These may be papillary, of alveolar type or of Hürthle cell type. They often give indication of origin from pre-existing adenomas, although not infrequently the development of the tumor has destroyed all evidence of the initial focus and the existence of a pre-existing adenoma may be deduced only from the history given by the patient.

The first subgroup of adenocarcinomas is the papillary form. This frequently invades the thyroid gland and adjacent normal tissue. The epithelium is variable in size and shape, usually with fairly well-defined cell borders. The epithelium tends to heap up rather than to form a single well-defined layer as is the case in the papillary cystadenoma. Occasionally, follicles and colloid may be present in the tumor. About 80 per cent of the patients bearing these tumors survive five years.

The alveolar type of adenocarcinoma is less differentiated and is made up of masses and strands of epithelial cells. The stroma is variable in amount. Here and there definite follicles are formed. These rarely may contain colloid. In this group only 27 per cent survived five years.

The rarest of the adenocarcinomas is the Hürthle cell type, which resembles closely the Hürthle cell adenoma already described, with large, clear acidophilic cells, but the arrangement is irregular, and invasion of adjacent thyroid tissue occurs. Mitoses, while not abundant, occur occasionally. The highly malignant carcinomas of Group 3 vary widely in appearance. The undifferentiated carcinoma simplex or small cell carcinoma occurs in two distinct forms; the compact form is readily recognizable by its masses of anaplastic epithelial cells without formation of follicles or of lumina. There is usually a high degree of mitotic activity. The diffuse type is much more difficult to recognize and is frequently confused with lymphoma or even chronic thyroiditis. The cells of the tumor are widely scattered. They are small with scanty cytoplasm and a rather small pyknotic nucleus. The stroma is rather dense, and the cells of the tumor are irregularly scattered through it, replacing much of the normal thyroid structure and extending out into the surrounding tissues. To render the picture more confusing, there may be scattered lymphocytes and macrophages present in the stroma as well. Fortunately, there are usually some small clusters of the cells

arranged in characteristic epithelial pattern. In this group only 22 per cent survived.

The giant cell carcinoma, sometimes called carcinosarcoma, is the most striking of the thyroid malignant tumors. Its large, bizarre cells and irregular mitoses make it easily recognized upon microscopic examination. It tends to occur in women about 50 or 60 years of age. It is very rapidly growing, extending widely and not infrequently compressing the trachea. The texture of the tumor is soft and meaty, rather more suggestive of a sarcoma than of a carcinoma.

In addition to these more frequent carcinomas of the thyroid, there are three malignant tumors which occur there very rarely. First, the true fibrosarcoma which may be recognized by the fact that its cells form fibroglia and collagen fibrils. Second, epidermoid carcinomas occasionally develop, either from epithelial nests or by metaplasia of thyroid epithelium. The third type is a true lymphoma of the thyroid, which must be differentiated from both the struma lymphomatosa of Hashimoto and the carcinoma simplex of diffuse type. Its appearance and behavior is comparable to that of lymphomas occurring elsewhere.

TUMORS OF THE FEMALE GENITAL TRACT*

RICHARD W. TE LINDE

Chief Gynecologist, The Johns Hopkins Hospital, Baltimore

I WAS asked by the Committee on Medical Education to make my remarks of a practical nature since most of you in the audience are engaged in the practice of general medicine. To this I gladly acceded. The general practitioner still represents the backbone of the American medical profession and by his excellence or mediocrity our present system of medical care stands or falls. Meetings such as these held during this fortnight are essential to keep the men who first see the patient abreast of progress in the various medical specialties. If I can add just a little to your practical knowledge in the field of genital tumors, I will feel well repaid for my efforts.

The female genital tract is particularly prone to the development of a variety of neoplasms. Consider the variety of tissues in the genital tract. The vulva, the vagina and the vaginal portion of the cervix are covered with stratified squamous epithelium. The cervical canal, the uterine cavity and the tube are lined with columnar epithelium. The ovary is covered with a special epithelium known as germinal epithelium. Within the ovaries are embryonic epithelial nests, the granulosa cells of the follicles, the lutein cells and, finally, the totipotent cells within the follicles, the ova. All of these organs also have mesodermic tissue, fibrous tissue and muscle from which benign and malignant connective tissue tumors may arise. Consider also that these tissues are frequently subjected to the irritation of inflammation and that they are constantly subjected to the influence of the hormones. There is constant activity during the monthly cycle in the ovaries, tubes and uterus of the sexually mature woman. During pregnancy there is an overwhelming hormonal stimulation which causes growth and alterations of all the pelvic tissues. There is, then, little wonder that the limits of physiological growth are often exceeded and pathological growths develop.

* Given October 14, 1946 at the 19th Graduate Fortnight of The New York Academy of Medicine.

In making a rapid survey of the female genital tract I shall start at the vulva and progress upward. The vulva is occasionally the site of benign growths, such as lipomas and fibromas. Rarely, they become so large that they interfere with sitting, walking and coitus and removal becomes necessary. Cancer of the vulva is more commonly encountered than these large benign tumors but still must be classified as a rare tumor. It represents about 3 per cent of genital malignancies. It usually appears as a small lump or ulcer which often requires biopsy to establish the diagnosis. If properly treated with radical vulvectomy and radical resection of the inguinal and femoral glands the five year salvage rate is as high as 58 per cent. Irradiation therapy is much less satisfactory and the post-irradiation burning sensation of the vulva may make the victim extremely uncomfortable.

Perhaps the most important point for us to remember about carcinoma of the vulva is that it is to some degree a preventable disease. In approximately half the cases of vulval carcinoma, it is preceded by leukoplakia. The symptom of leukoplakia is itching and every case of pruritus vulvae should be carefully examined for leukoplakic changes in the skin. When found, the area should be excised, even though it involves the entire vulva. The precancerous nature of leukoplakia has been proven beyond doubt. I have observed two patients with leukoplakia of the vulva who were not operated upon for good medical contraindications and who developed cancer directly under observation. Approaching it from a pathological angle, Smith and Graves found that in 21 vulvas removed for cancer, leukoplakia was found elsewhere in the vulva in 16 cases.

The vagina is too rarely the site of neoplasm to warrant much consideration here. Fibromas and papillomas are occasionally seen and equally rare is carcinoma. The latter is almost uniformly fatal. It cannot be successfully treated surgically. If sufficient irradiation is used to give reasonable hope for a cure, rectovaginal or vesicovaginal fistula will almost certainly develop.

The cervix is the point in the generative tract most susceptible to carcinoma. Benign polyps are also common. The incidence of malignancy in them is extremely low but when removed they should be sectioned to exclude microscopic cancer. Although the chance of malignant change occurring secondarily in a benign polyp is extremely small, occasionally endocervical cancer protrudes from the external os

and looks not unlike a benign polyp. The real importance of polyps lies in the fact that their initial symptom is usually intermenstrual spotting which is indistinguishable from that of cervical carcinoma. Whenever it occurs, speculum examination and cervical biopsy are indicated.

It seems that it should be an extremely simple matter to teach the medical profession that every woman over thirty with intermenstrual bleeding should be subjected to a speculum examination and cervical biopsy. And yet, these simple procedures are neglected every day. I now have under treatment a woman with cervical cancer who had seen three practitioners who refused, even at her insistence, to make a cervical biopsy. Such experiences are discouraging from the standpoint of education of the medical profession but they do indicate that much can be accomplished by direct education of women. The statistics of Norman Miller from the University of Michigan have made a great impression on me and I would that practitioners who see the patients first would be equally impressed. Miller found in a series of uterine cancers that an average of seven months elapsed between the appearance of the first symptom of cancer and the time the patient saw her family physician. That loss of time is the fault of the patient and perhaps it can be corrected by education of the public. But, four more months elapsed between the time the patient saw her family doctor and the time when she got under the care of one who was in a position to institute proper therapy. Thus a total of eleven months were lost and this loss of time usually spells the difference between success and failure in cancer.

I wish to say a few words about a phase of this subject in which I am especially interested. I refer to the early microscopic diagnosis of biopsy specimens. Since we are in a large measure ignorant of the cause of cancer and have no specific therapy for advanced cancer, it seemed to us that perhaps the greatest contribution that could be made within the bounds of the present state of our knowledge of these fundamentals would be along the line of early diagnosis. Accordingly, we have been making a vast number of biopsies of normal and abnormal cervixes, many of which were scheduled to be removed in the course of hysterectomies for fibroids. We believe it is now possible to diagnose cervical cancer in the preinvasive stage. We have found in the vast majority of the cases in which preinvasive cancer was found in the biopsy; that early invasive cancer can be found if the entire removed cervix is cut into blocks and many sections made. We have been impressed also with the

number of these cases in which, on careful questioning, slight intermenstrual bleeding was noted, especially after coitus. I am sure that most of you are not interested in the finer points of gynecological pathology but it is important for you to know that there are laboratories to which you can send your biopsies and which will give you an intelligent diagnosis. I do not mean that you can get an expert opinion from every general pathologist but there are laboratories in this city where specially trained gynecological pathologists can do this for you.

It is our belief that cancer of the cervix may remain in this pre-cancerous stage for months and even years before becoming invasive. If this is true, we have a recognizable cervical lesion which can be discovered in ample time to be cured. We base our belief in the long existence of cancer in the preinvasive stage on at least two facts. The average age of the women in our series was 36 years, whereas the average age of cancer of the uterus in general is 48 years. Furthermore, in two cases of advanced cervical cancer we discovered that we had in our laboratory previous biopsies. On reviewing the earlier sections we found the typical intra-epithelial lesions. In one instance the biopsy had been done $3\frac{1}{2}$ years before and in the other $8\frac{1}{2}$ years. At the Womens Free Hospital in Brookline the experience has been identical to ours. Among their cases of advanced cervical cancer they found four that had had biopsies years before which showed the typical intra-epithelial lesions. Incidentally, this experience of Smith's and ours gives strong support to the view that these early lesions are actually cancer, a point about which some doubt has been cast by some pathologists.

It has been our practice in the past six years to treat these cases of microscopic cancer by radical total hysterectomy. The operation which we do includes the removal of a liberal cuff of vagina with the cervix, but does not include lymph gland resection as in the typical Wertheim operation. We have chosen hysterectomy rather than irradiation for two reasons. Many of these cases occur in women in the third decade of life and we have chosen to save an ovary in some of them. Since the ovary is a late site of cervical cancer metastasis we have felt safe in doing this and our results have not caused us to regret it. In addition, we wished to check our diagnoses by cutting the entire cervixes into blocks for histological examination. At the time of our last check up three years ago all of the patients were well up to four years. We are now in the process of following up a much larger series.

I do not wish to convey the impression that our routine treatment of cervical carcinoma is panhysterectomy. We employ it only for these microscopic lesions. In general, radium to the cervix and deep x-ray to the pelvis have proven far superior to surgery in the treatment of cervical cancer. The five year salvage rate in the better clinics is in the neighborhood of 25 per cent.

However, there is an experiment being carried out now in the clinic of Dr. Joe Meigs at the Massachusetts General Hospital which should be watched by all of us with the greatest of interest because it is possible that the outcome of this experiment may change our present ideas. Meigs felt that the radical Wertheim panhysterectomy, which formerly carried a mortality of about 12 per cent, should be re-evaluated in the light of modern surgical measures, such as the frequent use of blood transfusion, plasma and fluids. Accordingly, he has performed the radical Wertheim operation on approximately 100 women with relatively early cervical cancer without a single death. It is too early to evaluate the five year salvage but Meigs has at least shown that the Wertheim operation is a relatively safe procedure today when modern precautions are taken. While we are awaiting the final answer from Meigs on five year salvage, I cannot condemn too strongly the rather common practice of many general surgeons of performing an ordinary panhysterectomy for this disease. The salvage from this practice is practically nil and Meigs' experiment is in no way intended to encourage these surgeons.

On progressing to the corpus uteri, let us first consider the commonest of all pelvic tumors, myomata. They are so common that it would seem that their correct treatment would be universally known and practiced. Yet, that does not seem to be case. If I were asked to offer a criticism of the present day treatment of myomata, I would say that too many of them are operated upon without justification. I could not select a better group before which to make this statement than one composed largely of practitioners for, after surgery has been advised by the surgeon, the patient often goes back to her friend, the family doctor, for her final advice. Recently I saw a woman with asymptomatic fibroids who had been advised by three prominent surgeons in a middle western city to have a hysterectomy. She returned to her practitioner for the final word. He told her that inasmuch as fibroids were benign tumors and since she was free from symptoms he could see no indication

for surgery. He sent the patient to me for another opinion. I thought that the family physician was quite right and the woman was spared a useless operation.

In general, asymptomatic fibroids require no treatment except insofar as they may be a factor in future childbearing. The corollary to this statement is that the older a woman is, the less likely will treatment be necessary. When future pregnancy is planned, however, the problem of the asymptomatic fibroid is one which requires the best of obstetrical and gynecological judgment. One must consider the probable effect of the tumor on conception and on the course of pregnancy and on delivery. One must weigh carefully the dangers of proceeding with a pregnancy in the presence of the tumors and the advantages and disadvantages of myomectomy, remembering always that a planned myomectomy may eventuate in a hysterectomy. If the myomatous uterus is already the site of pregnancy one must consider the possibility of an abortion, which may be quite complicated in a myomatous uterus. Also to be considered are the interference of the tumor with the birth of the child and the advantages of Cesarean section at term, with or without hysterectomy.

Aside from the relation to pregnancy, the indications for treatment are simply stated. Excessive bleeding, usually of the menorrhagic type, abdominal discomfort from pressure and distortion of the abdomen by the presence of a large tumor are the usual symptoms which necessitate treatment. Except when there is evidence of postmenopausal growth, the possibility of malignancy is seldom an indication for hysterectomy. The incidence of malignant change in the tumor is less than one per cent and the patient runs an equal risk from hysterectomy.

The symptom of bleeding from fibroids is worthy of a short analysis. It may be stated at the outset that the presence of blood coming from a fibroid uterus does not justify the assumption that the fibroid is responsible for the bleeding. This is true even when the bleeding is confined to the menstrual period. Multiple pathological lesions in the uterus are common and the fibroids may be quite incidental. When the abnormal bleeding is of the intermenstrual type, the chances are strongly in favor of the bleeding being due to a lesion other than the fibroids. It is a rule on our service to biopsy the cervixes of all women upon whom a hysterectomy for fibroids is contemplated when there is a history of intermenstrual spotting. We do this regardless of the innocent

appearance of the cervix. It has been surprising how many early cervical cancers we have uncovered in this way.

When postmenstrual bleeding occurs in the presence of a fibroid uterus, one should never assume that the fibroid is the cause of the bleeding. The chances are great that some other lesion is responsible for the bleeding and that lesion is very apt to be malignant. The next logical question is whether a fibroid can ever be responsible for postmenopausal bleeding. The answer is: Yes, but rarely. We have observed asymptomatic intramural fibroids at the time of the menopause work their way into the uterine cavity and cause even profuse bleeding after the menopause, making a hysterectomy necessary.

Carcinoma of the corpus uteri is only about one-eighth as frequent in occurrence as cervical cancer. It occurs, on an average, a decade later in life but in spite of being primarily a postmenopausal disease, it occasionally occurs in young women. We have seen a few cases in the fourth decade of life and our youngest case was in a Negress of twenty-two. I mention these occasional early occurrences only to remind you that intermenstrual bleeding can mean malignancy at almost any age. The diagnosis can only be made with certainty by curettage although one must strongly suspect it in bleeding postmenopausal women when the cervix looks normal.

Most everyone agrees today that the treatment of corpus malignancy should be some form of irradiation followed by total hysterectomy and double salpingo-oophorectomy. There is some difference of opinion as to whether irradiation should be given by x-ray or by intrauterine application of radium. It is probable that there is not much choice, but it should be remembered that, regardless of how irradiation is given, a large percentage of the irradiated uteri will show active cancer in the uterine cavity. Statistical studies have pretty well shown that irradiation plus surgery is better than surgery alone or irradiation alone. However, many of these carcinomas occur in very old women who are poor surgical risks and it is comforting to know that something can be accomplished by irradiation alone. The five year salvage from irradiation is in the neighborhood of 35 per cent which is about half that of irradiation followed by surgery.

The problem of ovarian neoplasm is comparable to that of tumors of the breast. Ovarian tumors, like breast tumors, are often silent growers and their removal is necessary before a verdict can be given regarding

malignancy. The incidence of malignancy in ovarian growths is so high that one cannot afford to take a chance on their benign nature. Furthermore, clinical experience, coupled with pathological studies, has demonstrated that ovarian tumors may be benign for years and finally become malignant. Consider, for example, the large ovarian tumor that has been responsible for noticeable abdominal enlargement for years. Suddenly, there is a rapid increase in size of the abdomen. The tumor is removed and on pathological examination it is found to consist chiefly of benign cystadenoma with areas of unmistakable carcinoma. A case such as this demonstrates that the history of long duration by no means rules out malignancy. Besides the danger of malignancy there are other potentialities which endanger life and increase operative risk. The commonest of these are torsion of the pedicle, infection and rupture.

The value of the admonition that all ovarian neoplasms should be operated upon depends on the ability of the examiner to distinguish between ovarian enlargement due to neoplasm and enlargement due to other causes. Slight enlargements, due to multiple small follicular cysts or single follicular or corpus luteum retention cysts, are common. To distinguish them from small neoplastic ovarian enlargements is not always easy, but it is important because of the possibility of malignancy, present or future, in all neoplasms of the ovary. Retention cysts often disappear spontaneously and their immediate removal would subject the patient in many instances to useless laparotomy. Multiple cystic retrogressing follicles may increase the ovary to two or three times the normal size. Such ovaries usually feel semisolid, and the surface is slightly nodular due to multiple small cysts. Single retention cysts are usually thin walled, often easily compressible, but at times they are tense. A thick-walled cyst is more apt to be neoplastic. Tumors that feel cystic in some areas and solid in others are liable to be malignant. A solid or cystic tumor with a nodular, irregular contour is frequently malignant. The solid smooth-surfaced tumor may be malignant, but may also be a fibroma. In spite of the greatest tactile skill, there are occasions when doubt will exist as to whether an ovarian enlargement is due to a retention cyst or a neoplastic cyst. Such cases should be watched at monthly intervals. Retention cysts may persist or disappear; the true neoplasm usually can be detected due to increase in size. The palpation of irregularities on the surface of the tumor is cause for suspecting papillary outgrowths that indicate neoplasm, and one should bear in mind that

all papillary tumors are potentially malignant. When one becomes reasonably certain that one is dealing with a neoplasm, a laparotomy should be done. When considerable doubt exists the decision may be made by direct visualization of the tumor through the culdescope.

Because ovarian neoplasms often grow silently, it is common to have the patient present herself for examination with signs of advanced ovarian malignancy. The silent growth of ovarian neoplasms constitutes one of the greatest reasons for periodic routine pelvic examinations. Abdominal pain or abdominal enlargement is the symptom that frequently brings the patient to the physician. These symptoms often mean spreading of the neoplasm beyond the ovaries with peritoneal implants and ascites. Pemberton found that 36 per cent of the ovarian carcinomata were inoperable when first seen. The question of laparotomy, when there is obvious advanced ovarian cancer, should usually be answered in the affirmative. When the patient's condition is very poor, peritoneoscopy with biopsy to confirm the diagnosis may suffice, but when the patient's general condition warrants it, she should be given the benefit of a laparotomy. Not infrequently a seemingly inoperable growth may be removed completely or nearly completely, and the patient remain well for years. The cure of a patient by incomplete removal of a malignant growth seems contrary to the usual principles of surgery and pathology, but we have observed cure even without postoperative irradiation. Furthermore, there is a group of papillary ovarian tumors that implants small papillary growths in a widespread manner over the peritoneum. These tumors are associated with marked ascites. Before operation, and even at the operation, they cannot be distinguished with certainty from truly malignant tumors, and yet after a complete pelvic operation with removal of the parent tumor, the implants retrogress and the patient remains permanently well. To refuse surgery in such a case, on the grounds that the ascites indicates inoperability, might withhold from the patient the chance of a permanent cure.

Benign unilateral ovarian neoplasms may be cured by unilateral oophorectomy, and this is the proper therapy in young individuals provided the opposite ovary appears to be normal. The tendency of certain types of benign ovarian tumors to bilaterality is well known. Suffice it to say here that the opposite ovary should be carefully examined for evidence of a small growth. In case of doubt, a biopsy and frozen section may be advisable. In menstruating women of forty or over the

preservation of the opposite ovary, although desirable, is not as essential as in younger women, and one might remove the opposite ovary on less evidence than would be required in a younger individual. It is a good rule to have an assistant in the operating room open every apparently benign ovarian cyst after removal. If intracystic papillomas are found with an appearance at all suggestive of malignancy, a frozen section should be made, especially in younger women in whom the preservation of the remaining ovary is very desirable. After the menopause, it is our custom to remove the opposite tube, the ovary and the uterus even though the unilateral tumor is benign, provided the patient's condition does not contraindicate the necessary added surgery.

When the ovarian neoplasm is obviously malignant, a hysterectomy and a double salpingo-oophorectomy are done routinely. The importance of removal of both ovaries in all cases is emphasized by the findings of Norris and Murphy. These investigators discovered that when one ovary was grossly malignant at operation and the other grossly benign, in 17.5 per cent the benign-appearing ovary proved to be malignant when examined histologically. A total hysterectomy is preferred to subtotal, but in some instances, when the tumors are fixed and the operation difficult, it is wise to do the lesser operation, rather than increase the operative risk by removing the cervix.

Most ovarian tumors are resistant to x-ray therapy; it never should be employed as a substitute for surgery. When a tumor is completely inoperable, x-ray may be resorted to, although the results are almost always disappointing. Very rarely, however, does one see a far-advanced or recurrent ovarian neoplasm melt away under ray therapy and the patient remain well for many years. The value of postoperative irradiation is still debatable. The literature is contradictory, with the weight of evidence slightly in favor of postoperative irradiation. It is our custom to irradiate postoperatively those cases in which there is obvious carcinomatous tissue left at operation, as well as those cases in which there is some question as to the completeness of the operation. We do not feel that statistical results justify the routine postoperative use of x-ray in those cases in which there is every evidence of a clean and complete surgical removal; nor do we irradiate those patients in whom massive carcinoma has been left at operation and whose general condition is very poor.

TUMORS OF THE BREAST*

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CARCINOMA of the breast is the commonest type of serious malignant disease in the female. Tumors of the breast are important to consider only for two reasons: first, the fact that they may be confused with carcinoma; second, that they may be precancerous conditions. Although these are the chief reasons for discussion of the other types of breast tumor, there are certain features of interest in many breast tumors which merit consideration.

In the breast, as elsewhere in the skin and subcutaneous tissues, there may occur a variety of benign and malignant tumors which are not essentially mammary in origin. Thus, there may be neoplasms of the skin, and also such benign tumors as lipoma, fibroma, hemangioma, and the like. These are of importance only in so far as they may be confused with intrinsic mammary tumors; and in the fact that they may participate in the extraordinary physiological changes which involve the breast itself during pregnancy and lactation. One illustrative case may suffice; an extensive cavernous hemangioma of the breast in which arterio-venous communications developed during pregnancy, resulting in a rapid increase in size, a bruit and thrill; and seriously threatening the cardiovascular equilibrium.

In consideration of benign conditions peculiar to the breast, mention must be made of supernumerary breasts, and islands of breast tissue. These are commoner than is usually supposed. They may manifest themselves for the first time during pregnancy or lactation, as painful swellings in the axilla, or along the border of the pectoral muscle. Sometimes they overlap the breast itself, and appear as a separate lobulation of tissue near the lower border, or more rarely the upper outer border of the normal breast tissue. These islands of supernumerary breast tissue may become carcinomatous, and probably do so as readily as do normal breasts. They may account for some of the instances of apparently

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primary breast carcinoma in the axilla without evident involvement of the breast itself. Galactocele, a large solitary cystic mass noted during or following lactation, is rarely encountered although it is described in all textbooks dealing with the breast. It is possible that the cyst represents the ultimate evolution of an isolated and frustrated island of supernumerary mammary tissue.

Adenofibroma, sometimes called fibroadenoma, occurs as a rounded or oval, freely movable encapsulated tumor in the breast of young women as a rule. Histologically it appears to be made up of adenomatous acinar or duct elements with an abundant and dense fibrous stroma. These tumors are usually single, but may be multiple, and appear in both breasts. They are usually about one or two centimeters in greatest dimension when first observed but they grow significantly during pregnancy and lactation. They are most commonly found in underdeveloped small breasts. This fact may be due to some developmental or hormonal reason, or merely due to the fact that they are harder to find, and hence more easily overlooked, in larger breasts. A minor mystery surrounds their fate if they are not removed early. Certainly large tumors of this sort are rare; and the finding of such tumors in older women is most unusual. Rarely, a calcified tumor in older breasts may be interpreted as the end stage of adenofibroma; but it is at least a tenable conjecture that the tumors may regress in later life. It has been suggested that these tumors may become malignant, and develop as sarcoma. However, since sarcoma is a very rare tumor of the breast, and adenofibroma is relatively common, this possibility does not appear to be very likely. A disseminated and non-encapsulated form of this disease, termed adenofibrosis, is now described, and distinguished from the group of generalized breast abnormalities formerly considered together as chronic cystic mastitis. Fibroadenomas, and especially adenofibrosis, may result in symptoms in relation to the menstrual cycle; especially in tenderness and transitory increase in prominence during the premenstrual stage, but as a rule the tumors are symptomless. Excision is usually desirable to establish the diagnosis and it is all that is necessary for treatment although the possible development of similar tumors in the same or other breast warrants follow-up observations.

Nodularity of the breasts, usually symmetrical, most pronounced in the upper outer quadrants and commonly associated with discomfort and engorgement during the premenstruum, is a functional disorder,

presumably related to hormonal disturbance, and important only in exciting apprehension in the patient, and sometimes giving rise to symptoms severe enough in themselves to require an attempt at relief. Unfortunately, attempts at therapy through administration of hormones are not often successful.

Another condition of the breast probably closely related to the hormones, is so-called chronic cystic mastitis. Numerous names have been proposed for the condition; and it is obvious that several different processes are described under this general designation. Cyst formation varies greatly, from multiple minute cysts to one or a few large ones; and there is every degree of epithelial activity from virtual atrophy to a high degree of active hyperplasia. Sometimes there is a relation of manifestations or symptoms to the menstrual cycle, but more often there is no definite relationship. Warren studied the late results in patients in whom this condition had been discovered in partial excisions of breast tissue, and concluded that the incidence of cancer in these patients in later life far exceeded the normal expectancy. He concluded that the condition is definitely precancerous. However, the likelihood of the development of cancer is not so great as to warrant the general recommendation of bilateral simple mastectomy as a prophylactic procedure in these cases. A reasonable program consists in careful surveillance, with exploration at any time that particular masses appear to be open to suspicion.

Intraductal papilloma is a condition first indicated and suspected by the occurrence of a bloody discharge from the nipple. On palpation, often a dilated duct can be felt beneath the edge of the areola. There has been some dispute as to whether these intraductal papillomas are precancerous lesions. Certainly, some carcinomas of the breast originate in this fashion, and it is a problem for the pathologist to decide which of the tumors are benign, which precancerous, and which represent early intraductal carcinoma. The condition is usually multiple and diffuse; and the only certain prophylactic against cancer would be bilateral mastectomy. Alternatively, a policy of frequent observations may suffice to detect carcinoma at an early stage, if it should develop.

Papillary cystadenoma is a similar process, probably involving the acinar rather than duct epithelium, and occurring in the more peripheral parts of the breast. These tumors are more often single, and may attain some considerable size before they are detected. They do not communi-

cate with the ducts, and hence do not present any discharge. They can be definitely regarded as precancerous, and breasts from which they have been excised should be kept under careful observation postoperatively.

Sarcoma of the breast is a relatively rare tumor, in general behaving as fibrosarcoma, although several histological types are described. Our experience with these tumors at the Pondville Hospital was summarized by Rogers and Flo. Surgical removal of the entire breast and fascia of the pectoral muscle is considered sufficient in most cases, although axillary metastasis has occurred in some types of the disease. Inadequate operations invite local and refractory recurrences, with involvement of the chest wall, pleura and lung.

Carcinoma of the breast is a disease of major importance, and the foregoing account of other conditions is important only in so far as they may be confused with carcinoma, or as they may be implicated as precancerous conditions. It may be stated at the onset that a mass in the breast is carcinoma until it has been proved to be innocent. A few years ago we made a study of all the breast operations at the Pondville Hospital in a year, comparing the surgeon's preoperative diagnosis with the pathological report. The gross error in clinical diagnosis was 22 per cent. Others may be more alert or astute in diagnosis, but the fact will remain that there is a considerable margin of error in clinical appraisal of masses in the breast. Since it is axiomatic that early treatment is most likely to succeed in mammary carcinoma, it follows that it is better to "look and see" than to "wait and see," in dealing with a mass in the breast.

Not only is the diagnosis of carcinoma of the breast difficult, but there is also a wide margin of error in the diagnosis of the presence of axillary node metastasis. The diagnosis of the presence of supraclavicular metastasis or of remote dissemination, is equally subject to wide error. However, an attempt should be made to appraise the extent of the disease in order to plan rational therapy.

Little need be said in regard to signs and symptoms of mammary carcinoma. The presenting manifestation in nearly all cases is a mass, discovered accidentally by the patient. It is ironical that in a region that lends itself so readily to inspection and palpation, the tumor is often far advanced when first discovered. Rarely, a bloody discharge, axillary metastases, or remote manifestations are the first presenting

symptom. Adherence or puckering or dimpling of the skin, often elicited only by skilful and painstaking examination, is one of the surest diagnostic criteria, although even this finding is not pathognomonic. Skin involvement, ulceration, fixation to the pectoral fascia, skin nodules, and swelling of the arm are late manifestations; along with the evidences of diffuse dissemination.

The treatment of mammary carcinoma most promising for cure remains radical surgery. Several attempts have been made to establish radiation therapy as the equal or superior to surgery but in no instance has it been possible to show results as uniformly satisfactory as those achieved by surgery. Similarly, there have been reported series of attempted cure by simple mastectomy, or by a subradical procedure which preserves the pectoralis minor muscle; but these procedures cannot stand comparison with the results of radical mastectomy.

There has been a growing critical evaluation of criteria of operability, and an increasing awareness of the prognostic significance of some of the clinical characteristics of the tumor. The gravity of inflammatory carcinoma has long been recognized, and this condition is generally considered to be hopeless, and to contraindicate radical surgery. A few years ago we made a study of other clinical characteristics of the primary disease correlated with the prognosis, such as the size of the lesion, the degree and character of skin involvement, the extent of axillary involvement, the age of the patient, and similar presenting manifestations. Haagensen and Stout have recently offered a similar study in greater detail. Observers are in general agreement as to the graver prognosis in younger women, the extremely bad prognosis associated with pregnancy and lactation, and the lessened chance of cure associated with evidences of local or axillary extension and involvement. These conditions must be considered as relative rather than absolute contraindications to operation, and an occasional cure may result even when markedly adverse conditions apparently prevail. Thus the criteria of operability are relative rather than absolute; and indeed radical surgery may occasionally be employed for palliation in the face of absolute contraindications such as demonstrable remote metastases.

It is likely that part at least of the progressive improvement in the end results of radical operation are to be attributed to improved selection of cases suitable for operation. Other factors in improving end results are a more favorable group; in that patients as a result of educa-

TABLE I

RESULTS OF RADICAL SURGERY
CARCINOMA OF THE BREAST—MASSACHUSETTS GENERAL HOSPITAL

<i>Period</i>	<i>Percentage Cures</i>
1894-1904	19
1911-1914	27
1918-1920	30
1921-1923	35
1924-1926	41
1927-1929	43
1930-1932	45
1933-1935	51

tion seek and secure proper medical advice at an earlier date. There has also been a progressive improvement in operative technique, or at least a dissemination of proper technique so that it is more regularly employed by a greater group of surgeons.

End-result studies have been carried out at the Massachusetts General Hospital on the patients operated upon for carcinoma of the breast since 1894. Table I shows the results in terms of 5 year cures for various periods.

It is noteworthy that although preoperative and postoperative x-ray therapy was employed sporadically, at no time could this practice be demonstrated to improve the results; and the procedure has been abandoned, except when it has been necessary to leave obvious malignant disease behind after operation in a poorly selected case. It is also noteworthy that the operations are performed by a large number of surgeons, and in recent years in an increasing number of cases by the resident staff. The operation has uniformly been a radical operation, with removal of both pectoral muscles and the axillary contents. It has not been necessary to employ skin grafting to effect closure except in rare cases; and it does not seem necessary or desirable to develop parchment thin skin flaps as advocated by some writers. The efficacy of the local operation is attested by the fact that operative field recurrences were only 11 per cent in the most recently studied series. Postoperative deaths, due to cardiac complications, pneumonia, sepsis and pulmonary embolus, were 2 per cent in the same series of cases.

Certain factors of significance in the prognosis should be emphasized. When the disease is limited to the breast, 75 to 80 per cent of cases are five year cures. When the axilla is involved, the cures drop to 33 per cent. The grade of malignancy, based on criteria first formulated by Greenough, is of great importance. Carcinomas of higher grades of malignancy show a higher incidence of axillary metastasis and a lower curability than do lower grades of comparable extent. There is also a greater incidence of local recurrence in cases of higher grade of malignancy.

The prognosis is definitely better in the older age group, partly because the younger women exhibit cancers of higher grades of malignancy, as a rule. Small carcinomas offer a better prognosis than large carcinomas, and skin involvement is definitely a factor of increased gravity. In our most recent series a biopsy performed at the time of operation nearly doubled the likelihood of recurrence in the operative field. The extent of axillary involvement seems to be of great importance. While the cases without any involvement show a high degree of curability, those with a definite finding of only one or two metastatic nodes are nearly as favorable; and it is only in the group with multiple nodes involved that the poorer prognosis of node metastasis is manifested.

It is well recognized that freedom from evident recurrence for five years does not constitute an absolute cure, but this period does give an opportunity to appraise the results of treatment, and permits relatively early evaluation of trends in the results. It is also well to emphasize that there is still a large but fortunately diminishing group of patients who are inoperable when first seen. For the recurrent and primary inoperable cases it is necessary to resort to palliative measures. The most effective palliation of the local manifestations of disease consists in radiation therapy. The efficacy of artificial menopause in the younger women with recurrences has long been recognized. The results of this procedure are most marked in the patients with skeletal metastases. More recently the older age group has shown a promising response to the administration of estrogens, or of testosterone. While the mechanism of the improvements in these cases is obscure, there is reason to confide that great advances will be made in their use, and that increased understanding may shed light on the problem of carcinoma of the breast.

RECENT OBSERVATIONS ON THE
DYNAMICS OF THE PULMONARY
CIRCULATION *

A. COURNAND

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THE essential function performed by the pulmonary circulation is to transfer blood from the right to the left ventricle and thereby to bring it into intimate contact with alveolar air. Still another function has been assigned to the lesser circuit, namely the storage of blood in the pulmonary vessels. Blood stored in the lungs could be used as an emergency reserve to help fill the left ventricle when sudden increased demand in systemic blood flow is not paralleled by an increased venous return to the right heart and would, if need be, damp the effect of unequal discharge of both ventricles.

For many decades physiologists have tried to decide whether blood flow, pressures and volume variations in the pulmonary circulation are the expression of the passive position taken by this circuit in the general phenomena of the vascular system or whether they are affected by changes in pulmonary vascular resistance regulated by an active vasomotor system. I shall attempt in this presentation to discuss, in a limited way, our present day knowledge of this problem in the light of recent physiologic and physiopathologic evidence.

The two chief characteristics of the dynamics of the pulmonary circulation may best be stated as follows: (a) the blood flow through the lungs is identical to the blood flow through the entire systemic circulation, except for momentary differences, (b) the pressures in the right ventricle, pulmonary artery and capillaries are lower than in corresponding structures of the systemic circulation.

From these characteristics several facts may be deduced. First: the energy developed by the right ventricle in performing its mechanical work, i.e., stroke volume times mean pressure in the pulmonary artery,

* Under a grant from the Commonwealth Fund.

Read at the Stated Meeting of The New York Academy of Medicine, March 7, 1946.

is much less than that developed by the left ventricle. This explains the unequal muscular development of both ventricles.

Second: the small rise in pressure in the pulmonary artery during ejection is due to its greater distensibility in proportion to its capacity as compared to the aorta. Pressure-volume diagrams obtained with sections of both large vessels bear out this fact directly,¹ while measurement of pulse wave velocity² (3 meters per second in the pulmonary artery of the dog as compared to 4-5 meters in the aorta) confirms it indirectly.

Third: the resistance to flow in the pulmonary vessels is much less than in the systemic vessels, the mean pressure difference between the pulmonary artery and the left auricle being $1/5$ of the mean pressure difference between the aorta and the right auricle. This low resistance is chiefly related to particular details of structures of the vessels: (a) the arterioles are few and their walls show very little smooth muscle, (b) the precapillaries are numerous and very large, sometimes larger than the arterioles, (c) the capillaries are short, with remarkable ability to increase their capacity by simple distention, (d) the veins are short and very distensible.

Fourth: the pulmonary circulation time must be short and the time of exposure of blood to alveolar air, likewise very short.

Blood pressures, blood volume, and circulation time in the pulmonary circulation of dog and normal man. One of the chief obstacles to accurate measurements of pressures in various parts of the pulmonary circulation of dogs lies in the difficulty of access to these parts and the abnormal physiologic conditions under which measurements have usually been obtained. Very recently, Hamilton, Woodbury and Vogt³ have developed a method which permits the recording of pressures in the pulmonary artery and vein of unanesthetized, intact dogs, several weeks or months after their recovery from an operation during which the distal ends of special cannulae were placed in contact with the pulmonary vessels, while their proximal ends were sewn under the skin of the thoracic cage; these cannulae served later as a guide for the introduction into the vessels of needles connected to manometers. By this method pressures in the pulmonary artery of several dogs averaged 37/10 mm. Hg. with a mean pressure of 20 mm. Hg., while the average pulmonary vein pressure varied during one cardiac cycle between 12 and 2 mm. Hg. The pressure gradient between artery and vein, largest during early systole, reached practically zero at the end of diastole,

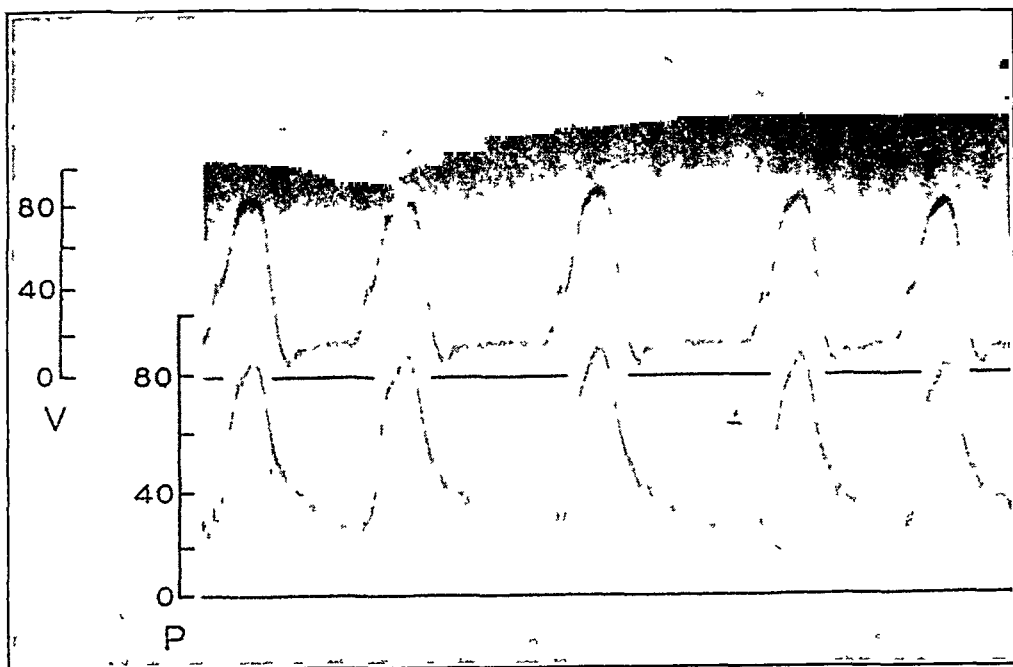


Fig. 1. Simultaneous blood pressure tracings in the right ventricle (top) and the pulmonary artery (bottom). In this and the following records scales are in mm Hg. (For description of this and of the following figures see text.)

another evidence of the small resistance to flow in the intervening arterioles and capillaries. In the course of many experiments they observed that pressure in the pulmonary artery rose with larger output from the right ventricle, while pressures in the pulmonary veins increased with some lag; but that a rise in pulmonary vein pressure closely followed increased resistance in the systemic circulation.

With Bloomfield, Lauson, Breed, and Richards⁴ we have measured pressures in the right ventricle in 14 normal human subjects under metabolic conditions which were nearly basal, the blood flow in this group averaging 3.6 liters/min/m²B.S. as compared to a standard figure of 3.1 liters. The ventricular systolic pressure averaged 25 mm. Hg. ranging from 18 to 30 mm. Hg., the pulse pressure, i.e., the difference between diastolic-filling pressure and peak of systolic pressure, ranged within the narrow limits of 21 to 27 mm. Hg.

Satisfactory records of pulmonary arterial pressures in man have, up to now, been difficult to obtain, on account of very marked superimposed oscillations due to motions of the catheter. In 4 normal individuals, where satisfactory tracings were recorded, the pressures averaged 25/8 mm. Hg. with a mean pressure of 15 mm. Hg. Fig. 1

illustrates an excellent record of simultaneous pressure tracings, in the right ventricle and pulmonary artery, obtained through a double lumen catheter in a patient in congestive heart failure where, therefore, the systolic and diastolic pressures were high.⁵

With a large blood flow and a low resistance, the mean circulation time is necessarily very rapid. After allowance is made with most methods used in experimental and clinical work, for transit of the chemical substance through the extra-pulmonary parts of its circuit, it is estimated that blood reaches the capillaries within 2 to 3 seconds after it has left the right ventricle, and reaches the left ventricle 2 seconds later. Roughton,⁶ very recently, using a new method in normal man, investigated the capillary time, i.e., the average length of time during each circulatory cycle in which gas exchange between capillary blood and alveolar air takes place. It is, approximately, $\frac{3}{4}$ of a second at rest and $\frac{1}{3}$ of a second during heavy work. Within this short interval a perfect or nearly perfect gaseous equilibrium, as is well established now, is reached, which speaks in favor of the high degree of efficiency attained by the pulmonary circulation in performing its essential respiratory function. Making apparently sound assumptions, Roughton went on to calculate the total area of the capillary walls and the total volume of capillary blood involved in this exchange—respectively 38 square meters and 60 cc. during rest. On the basis of the probably correct assumption that the capillary blood volume in the pulmonary vascular system constitutes, as in other regional vascular systems about 15 per cent of the entire volume, the circulating pulmonary blood volume under basal conditions would amount to 400 cc. or 8 per cent of the total circulating blood volume. This figure compares well with the value of approximately 10 per cent given by Kuno⁷ who measured pulmonary blood volume directly on dogs in the heart-lung preparation.

A summary of standard measurements of blood flow, pressures, pulmonary blood volume in normal man under basal condition is given in Table I. Circulating pulmonary blood volume, and pressure, in the lesser circulation, are, however, not static as would appear from this Table. They are continuously influenced by the output of the right ventricle, the resistance in the pulmonary circuit and the effect of back pressures in the pulmonary veins resulting from variations in left ventricular output. We shall, therefore, consider the dynamic relationship between flow, pressure, and circulating blood volume in the lesser circulation

TABLE I

SOME MEASUREMENTS OF THE PULMONARY CIRCULATION IN
NORMAL MAN, SUPINE AND UNDER BASAL CONDITION

Blood Flow	lit/min	5.5
	lit/min/m ² BS	3.1
<i>Pressures</i>		
<i>Right Ventricle</i>		
Syst/Diast ...	mm Hg	25/2
<i>Pulmonary Artery</i>		
Syst/Diast ..	mm Hg	25/8
Mean	mm Hg	15
<i>Capillary</i>		
Mean	mm Hg	between 8—2 (appx.)
(Oncotic)	mm Hg	25
Blood Volume as a fraction of Total Blood		1/10
Volume		

under varying physiological conditions, such as changes in position and in intrathoracic pressure.

Increase and decrease in pulmonary blood volume, according to the experimental work of Drinker, Churchill and Ferry⁸ are easily accommodated by the capacious vascular bed. The blood volume increases with larger discharge of the right ventricle and smaller discharges of the left and conversely decreases with smaller discharges of the right ventricle and larger of the left. Variations in the circulating blood volume within the lungs necessarily originate during the short periods in which, under normal physiological conditions, the two ventricular outputs differ. There is good evidence also brought out by the work of Hamilton and his co-workers,⁹ using the dye technique, that under physiologic conditions in man, pulmonary blood volume variations are positively correlated with stroke volume variations.

Measurement of the vital capacity, within the limits of accuracy of this procedure, is also an excellent means of demonstrating qualitative changes in pulmonary blood volumes, since Drinker, Peabody and Blumgart¹⁰ have shown that storage of blood in the lungs is at the expense of the air spaces. It is well known that vital capacity decreases in normal man as he moves from the standing or sitting to the recumbent position. In the latter position venous return from the abdomen and lower limbs

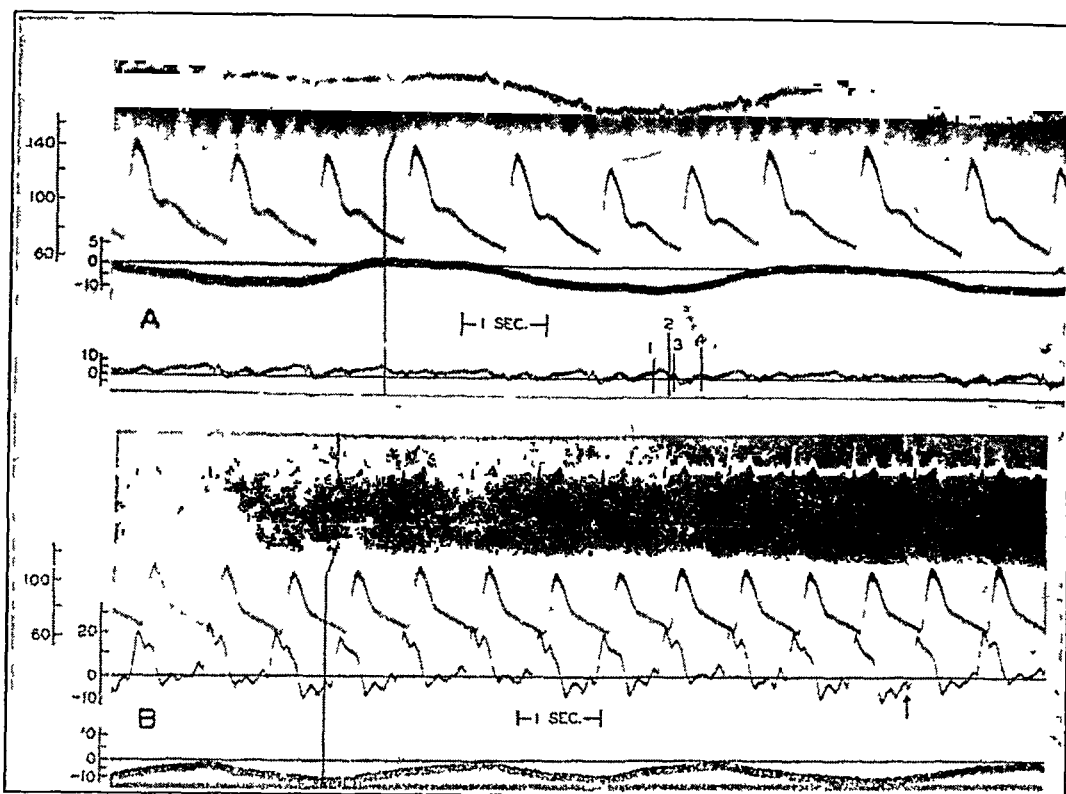


Fig. 2. Simultaneous blood pressure tracings in (a) femoral artery, pleura, and right auricle and in (b) femoral artery, right ventricle and pleura. Simultaneous electrocardiographic tracings at top of each record—vertical line indicates parallax between electrocardiogram and blood pressure tracings.

to the thorax is increased, the stroke volume of the right ventricle becomes larger, causing a rise in the pulmonary artery mean pressure and active congestion of the lungs. A convincing demonstration of the increase of the cardiac output in the recumbent position has been given by McMichael and Sharpey-Schafer¹¹ using the "Direct Fick" method. The importance of the increase of the venous return in the mechanism under discussion is stressed by the observations made in man by Hamilton and Morgan¹² and later by Dow,¹³ which indicated that the decrease in vital capacity associated with a change to the recumbent position is lessened or prevented by the application of pressure cuffs on the four limbs.

Influence of various types of breathing upon blood pressure and blood flow in the pulmonary circulation. In the course of still unpublished studies of the effects of intrathoracic pressure variations upon the dynamics of the pulmonary circulation in man done in collaboration

with Lauson, Bloomfield, Breed and Richards,¹⁴ and more recently with Motley, we have taken simultaneous pressure records in the right auricle and/or the right ventricle and the femoral artery, together with pneumographic tracings, during (a) quiet breathing, (b) deep breathing, (c) prolonged holding of breath in inspiration and expiration with opened or closed glottis and (d) intermittent pressure breathing. In a few cases with artificial pneumothorax, intrapleural pressures were recorded in addition. Examples of simultaneous pressure recording in the right auricle or ventricle, the femoral artery and the pleura in two cases of therapeutic pneumothorax during quiet breathing are shown in Fig. 2.

Interpretation of this and the following records in terms of blood flow variations stems directly from the extension to man, of Starling's law of the heart. If pressures in the right ventricle in successive cardiac cycles are measured exactly at the end of diastole and if the corresponding value of intrapleural pressure is subtracted from it, one obtains the effective diastolic (sometimes called net initial) pressure. This effective diastolic pressure is related to the degree of stretch of the filled ventricle. If the pulse pressure is then measured from the end of diastole to the peak of systole, the degree of response to the stretch and presumably the variations in stroke volume may be qualitatively estimated. An analysis of several hundred cardiac cycles of the tracings obtained in the patient illustrated in Fig. 2 (section B) during quiet and deep breathing has been made in this manner by Dr. Lauson, the result of which indicates a direct linear relationship between the effective diastolic pressure and the pulse pressure of the same beat. In most of our studies the pleural pressure is therefore unknown. However, the pulse pressure variations may be taken as indicating variations in stroke volume in the right heart and as the same argument applies to the left ventricle, variations in pulse pressure in the femoral artery may be interpreted as variations in left ventricular discharge, if in these short intervals the state of the peripheral vascular bed can be considered to be essentially unchanged. Since increase or decrease in peripheral vascular resistance would result respectively in an increase or a decrease in pulse pressure, blood flow remaining the same, this factor must also be taken into account in the interpretation of pulse pressure variation.

Using this method of analyzing tracings it would appear that in normal man during quiet breathing there is no evidence of unequal discharge of both ventricles. This confirms similar observations made by

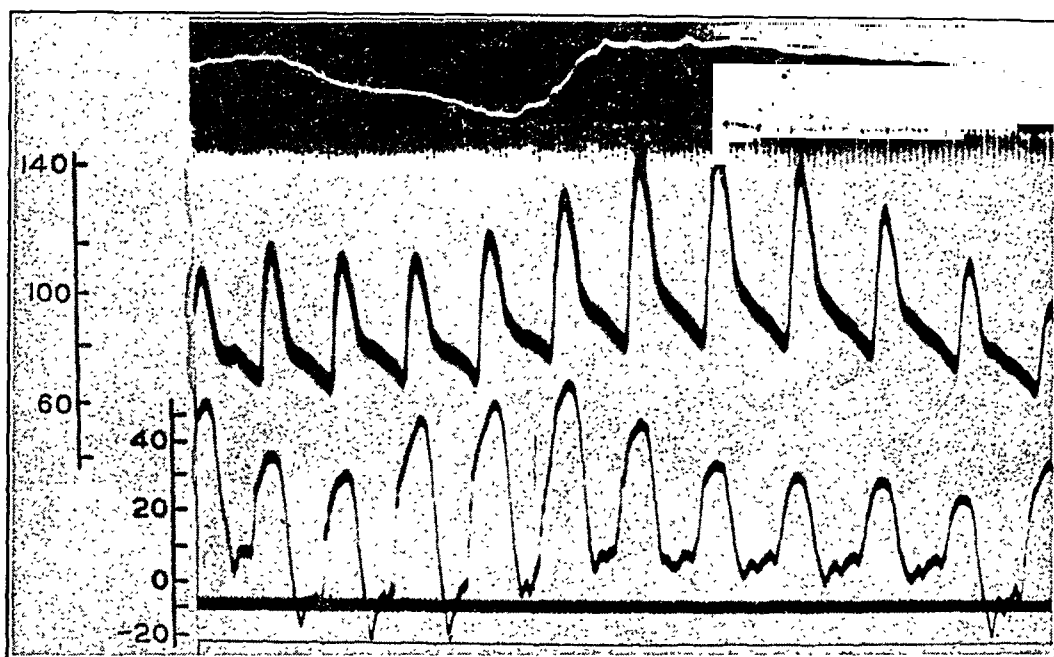


Fig. 3. Simultaneous pneumogram (top row), electrocardiogram (2nd row), blood pressure tracings in the femoral artery (3rd row) and in the right ventricle (bottom row) during deep breathing. Downward stroke of the pneumogram indicates inspiration—upward stroke—expiration.

Hamilton in animals.¹⁵ However, during deep breathing, the evidence is in favor of unequal stroke volume of the two ventricles. In Fig. 3 it is seen that during deep inspiration the pulse pressure in the right ventricle is very large, while it is small in the femoral artery; whereas, the reverse occurs during expiration, when the pulse pressure increases markedly in the femoral artery and decreases in the right ventricle.

The following interpretation may then be given: (a) during inspiration the fall in intrathoracic pressure favors venous return, filling of the auricle and right ventricle. With the consequent rise in ventricular output, the pulmonary arterial mean pressure increases and blood is forced through new capillaries, as the distended lung tends to create an increased resistance in the capillaries already perfused. At the same time less blood is displaced from the actively congested lungs into the pulmonary veins than is being received into the lungs from the pulmonary artery. (b) When the respiratory cycle is reversed, relaxation of the lungs by displacement of blood causes an increase in pulmonary venous return, and left ventricular output, as evinced by a rise in the femoral artery pulse pressure. Meanwhile, the higher intrathoracic pressure

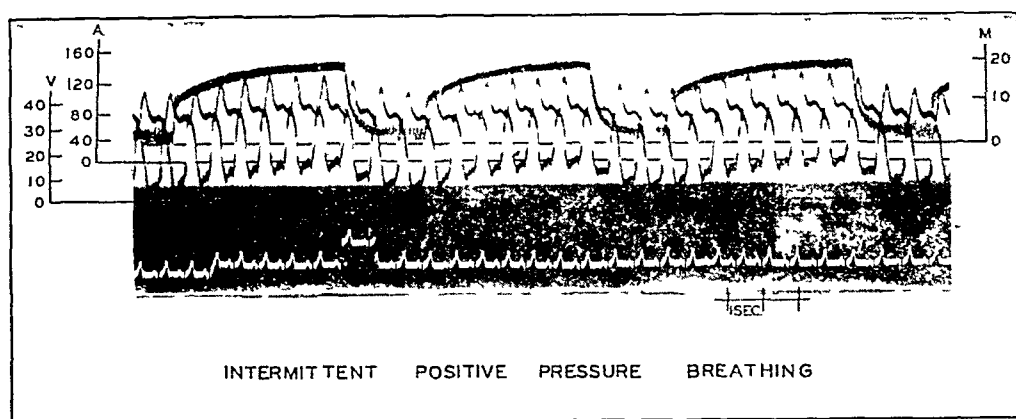


Fig. 4. Simultaneous tracings of mask pressure (M), and blood pressures in the femoral artery (A) and in the right ventricle (V) during intermittent pressure breathing.

decreases the venous return to the right auricle, causing a smaller discharge of the right ventricle.

The mechanism involved in intermittent pressure breathing with positive intrapulmonary pressure inflating the lung, followed by passive deflation, is exactly the reverse of the one just discussed in deep breathing. One typical example of intermittent pressure is illustrated in Fig. 4. The tracings were obtained in a normal young intern who volunteered for the study of a new type of artificial respiration apparatus. Inflation of the lungs under positive pressure and passive deflation were obtained through a special valve converting continuous positive pressure, supplied by a pressure tank, into an intermittent pressure transmitted through a mask to the lungs. It is easy to see the effect of the intrathoracic pressure increase and decrease upon the level of the pressure curves in the right ventricle and femoral artery. But only a beat to beat analysis of pulse pressure changes, in relation to the mask pressures, gives an idea of the magnitude of the probable unequal discharge of both ventricles. This relationship is illustrated in Fig. 5. It is seen that while pressure rises in the mask, the femoral pulse pressure becomes larger presumably as blood is forcibly displaced by the high intra-alveolar pressure into the pulmonary veins, thus increasing the left ventricular discharge. Meanwhile, the pulse pressure decreases in the right ventricle in spite of a marked increase in pulmonary vascular resistance; this points to a smaller discharge from the right ventricle, as the rising intrathoracic pressure causes a reduction of blood return from

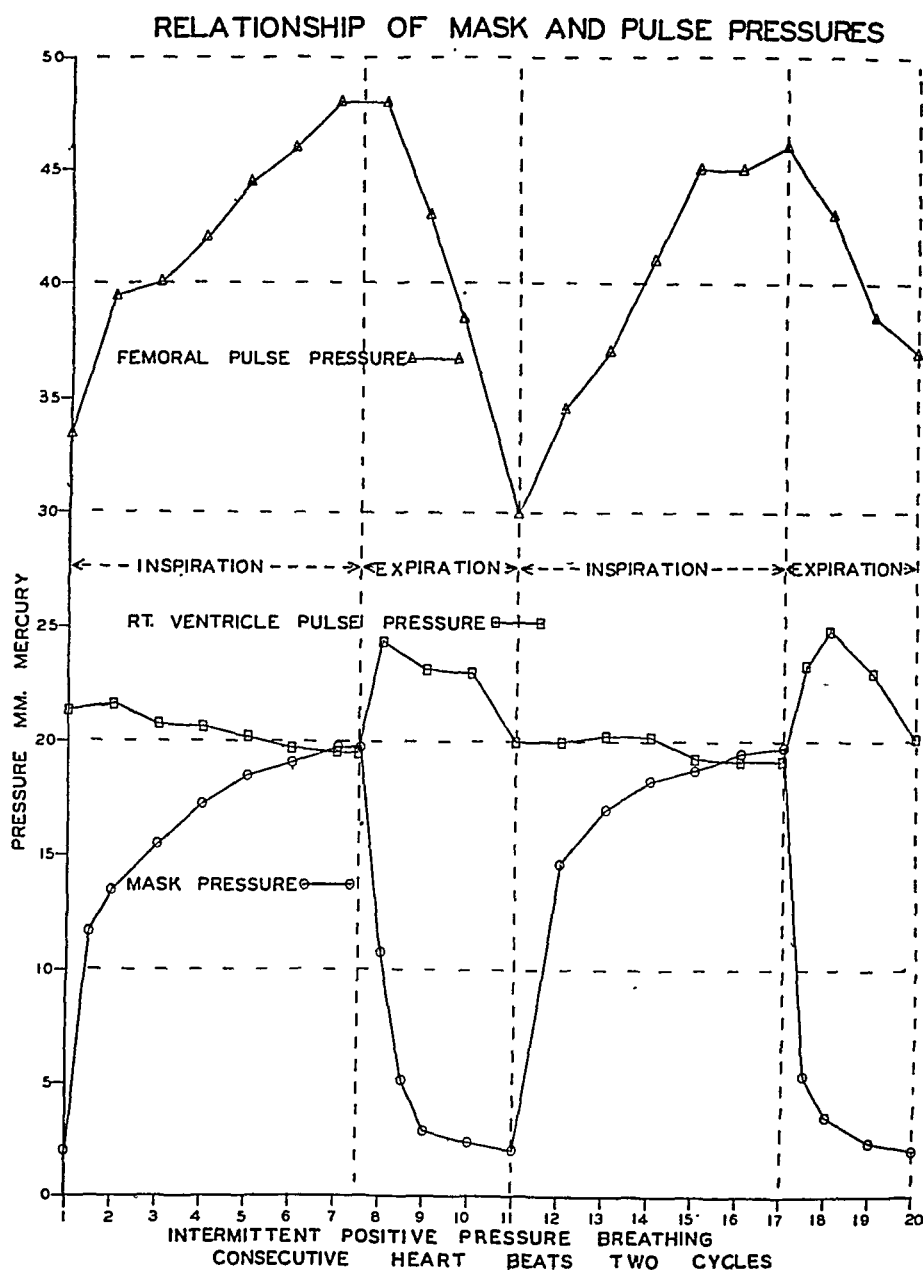


Fig. 5. Chart showing a beat to beat analysis of mask and pulse pressure changes illustrated in Fig. 4.

the large veins into the right auricle. During the short passive expiration the mask pressure falls rapidly, the lower intrathoracic pressure now favors venous return, hence, increased discharge of the right heart reflected in the marked pulse pressure rise. An increasing volume of blood is now held in the lung capillaries the capacity of which suddenly increases as the pressure in the alveoli drops. Therefore, the venous

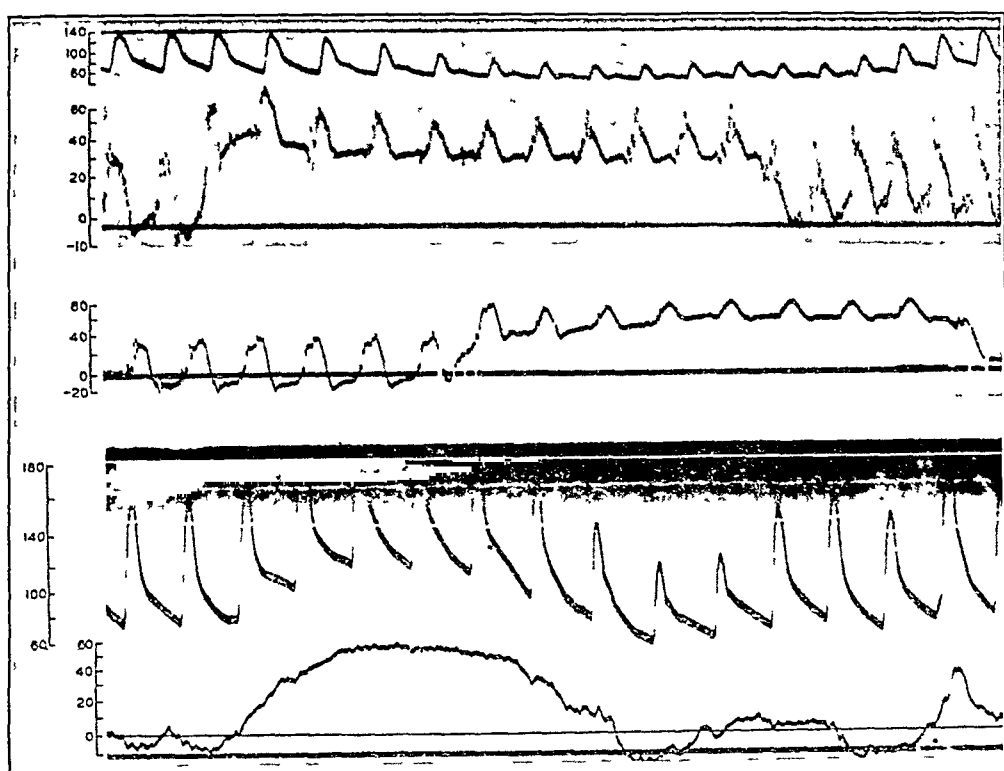


Fig. 6. Effects of a forced expiration upon blood pressure in (a) the right auricle and femoral artery (bottom row), (b) the right ventricle (middle row) and (c) the right ventricle and femoral artery (top row).

return to and the output of the left ventricle is lessened significantly as witnessed by the considerable reduction in the femoral artery pulse pressure.

The *modus operandi* of intrathoracic pressure variations upon flow, pressures and circulating volumes in the pulmonary circulation becomes clear from these studies: (a) changes in the general level of the pressure curves in the auricle, ventricle, pulmonary artery and veins, and even in the systemic large arteries are passive due to simple propagation of the intrathoracic pressure; (b) variations of the latter influence the venous return and, therefore, the discharge of the right ventricle; (c) finally, the state of distention or relaxation of the lung parenchyma in deep breathing and, in the case of intermittent pressure breathing, the variations of resistance to flow created by intra-alveolar pressure regulate the amount of blood stored, the size of the capillary bed perfused, and the return of blood to the large pulmonary veins. The effects of this pul-

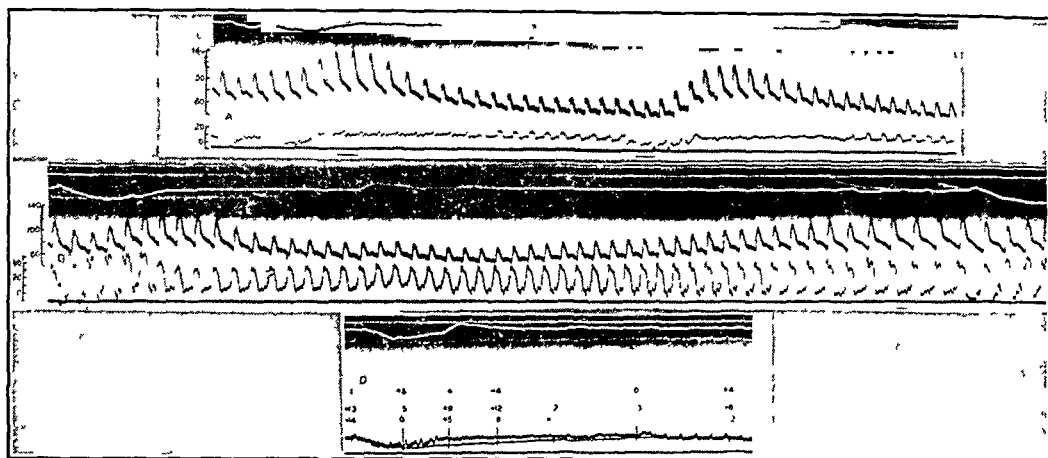


Fig. 7. Effects of a forced expiration maintained over a long interval of time upon the blood pressures in the right auricle and the femoral artery (top row), the right ventricle and the femoral artery (middle row) and the right auricle and a peripheral vein (bottom row).

monary factor upon the variation of vascular resistance in the intrapulmonary vessels are difficult to express quantitatively in man, since we lack the measurement of pulmonary vein pressure essential to determine the pressure gradient forcing blood through the vascular bed. Animal experiments carried out by Hamilton, Woodbury and Vogt³ indicate, however, that intra-alveolar pressure variations are effective in temporarily creating marked variation in vascular resistance.

With this background I shall now present briefly the effects of a forced expiration upon right heart and femoral pressures. At the bottom of Fig. 6 are shown tracings of pressures in the right auricle and femoral artery, recorded during a forced expiration of short duration against a closed glottis. The intrathoracic pressure increased markedly as revealed by the auricular tracing and the diastolic pressure level of the femoral artery, but at the same time the femoral pulse pressure became larger indicating greater discharge of the left ventricle. In the next two rows, the effects of the same type of breathing upon the right ventricle discharge are well illustrated by the sharp drop in right ventricular pressure during forced expiration and its rapid rise as inspiration is resumed. The femoral tracing of the first row in addition shows a marked reduction in the diastolic pressure level, associated with a considerable reduction in pulse pressure, indicating that the persistent decrease in output of the right ventricle is followed rapidly by a reduction in dis-

charge of the left.

Some questions regarding the adaptation of the entire circulatory system to such an extreme type of breathing, maintained over a relatively long interval of time are partly answered in Fig. 7. In the top row of this figure, we observe the effects of a prolonged expiration, similar to those just described. In the second row, a ventricular pressure tracing was substituted for the auricular. At first, while the forced expiration progresses, the right as well as the left, ventricular discharge is reduced; this is reflected by the diminishing pulse pressures. After 20 to 24 beats, the pulse pressure rises again, first in the right ventricle, and then in the femoral artery. The mechanism of this secondary rise in right ventricular output is tentatively illustrated in the last row. Simultaneous tracings of pressures in a peripheral vein and in the right auricle were here recorded during the course of a similarly prolonged forced expiration. The figures for pressure in the peripheral vein, and in the auricle, and for the pressure gradient between both indicate that during the Valsalva experiment the pressure in the auricle is higher than in the peripheral vein for a period of time of approximately 13 seconds in this instance; then as blood accumulates in the vein, its pressure progressively rises and presumably the consequent increase in filling pressure initiates the larger discharge of the right ventricle mentioned previously.

Role of the pulmonary vaso-motor system in the regulation of flow and pressures. In our discussion, so far, the active role played by the blood flow and the passive one played by the vascular bed have been emphasized. The question comes up now whether the vaso-motor system plays a part in the regulation of peripheral vascular resistance of the lung vessels. Since anatomists¹⁶ have demonstrated that there exists a dual nerve supply, sympathetic and parasympathetic, going to the muscular structures of the pulmonary vessels, it is in order to find out about its physiologic significance.

To the debate started in the last century and so thoroughly reviewed by Tigerstedt¹⁷ and Wiggers,¹⁸ Hamilton¹⁵ has recently brought new evidence denying that any active role is played by the vaso-motor system in the regulation of blood flow through the lungs in dogs. To a critical analysis of the probable inadequacies of the methods previously used by the proponents of an active vaso-motor system, in particular Daly,^{19,20} he has added experimental evidence acquired with his new

method of pressure recording³ wherein the pulmonary arterio-venous pressure gradient is measured directly in the unanesthetized intact animal. An analysis of the results of his experiment with drugs such as epinephrine, acetylcholine, amylnitrite, and histamine, led him to the following conclusion:¹⁵ (a) that the changes in arterio-venous pressure gradients, when they were present could always be related to changes in blood flow and, therefore, were not necessarily associated with changes in resistance, (b) that the lack of direct effect of the drugs as they were first passed through the pulmonary arterioles was in striking contrast to their immediate action on the systemic arterioles. Extending his argument to the physiologic action of exercise, Hamilton compared the latter effects upon the dynamics of the pulmonary circulation to the effects of the systemic vaso-dilator drugs. According to his views, which confirm previous experimental data obtained by Dunn,²¹ as soon as the vaso-dilatation of arterioles rapidly following the onset of exercise, has taken place, venous return and, therefore, pulmonary blood flow increases. However, the pressure in the pulmonary artery and the pressure gradient between pulmonary artery and vein rise very little: the resulting lower quotient of arterio-venous pressure gradient over blood flow then expresses a reduction in pulmonary vascular resistance created by the opening up of many new vascular channels and favoring a more rapid circulation time. A confirmation in man of this purposeful adaptation of the pulmonary circulation to a physiologically induced increase flow, lies in the figures given by Roughton,⁶ in the work previously mentioned, of the much shorter capillary time, during heavy work than during rest.

However, to discuss, whether the vaso-motor system plays a significant role in the regulation of the pulmonary circulation in man, we have to resort to indirect evidence, since we lack the essential measurement of arterio-venous pressure gradient. As a first evidence we may use observations which we secured during a study of the treatment of shock in man using the pressor amine methedrine. In Fig. 8 are shown tracings of pressures in the femoral artery and in the right ventricle recorded prior to and at short intervals following the intravenous injection of this drug. In addition cardiac output measurements were made immediately before the first series of tracings and shortly after the last. One notes that the diastolic and the pulse pressure in the right ventricle rose hardly more than by a few millimeters of mercury for

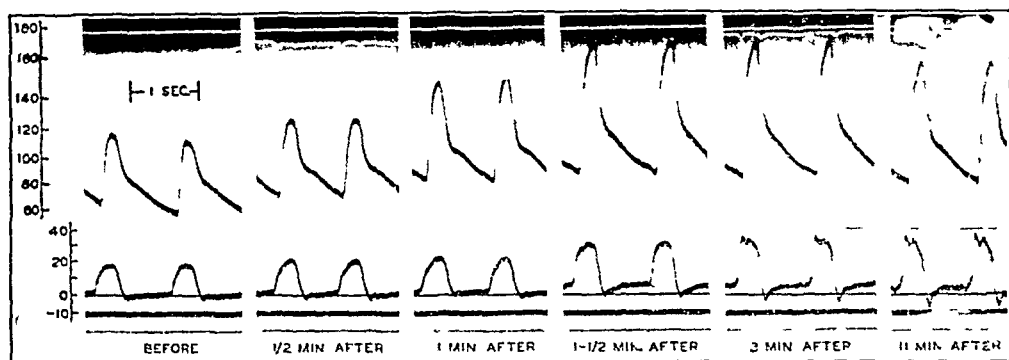


Fig. 8. Effects of the intravenous injection of the pressor amine, methedrine on the blood pressures in the femoral artery (top row) and in the right ventricle (bottom row).

the first $2\frac{1}{2}$ minutes while the pulse pressure and systolic pressure in the femoral artery increased by more than 20 mm. Hg. This would seem to confirm the observations of Hamilton on the absence of direct action of the vaso-constrictive drugs on the pulmonary vessels. The later changes in the right ventricular pressure can probably be explained on the basis of (a) an increased blood flow which, 14 minutes after injection, was approximately 20 per cent larger than the control value, or (b) backflow pressure in the pulmonary vein as a result of increase resistance in the systemic circulation.^{2,22} The second evidence is supplied by some observations, made with Lauson and Bloomfield on right ventricular pressures and cardiac output measurements in 5 cases, with systemic arterial hypertension and good cardiac compensation, who were under the care of Dr. Goldring and Chasis. While the average mean pressure in the systemic circulation was elevated to 128 mm. Hg., the normal being about 95 mm. Hg., the average systolic and pulse pressures in the right ventricle were at the respectively normal figures of 25 mm. Hg. and 23 mm. Hg. Although definite conclusions should await further investigation, it seems reasonable to conclude from these limited data that the biological substance thought to cause increased resistance in the arterioles of the systemic circulation had in these cases no effect upon the arterioles of the lesser circulation. As a third type of evidence we shall have recourse to some observations of change in the arterial oxygen saturation made by Jacobaeus and Bruce,²³ after complete blocking of one main bronchus in normal young volunteers. The marked reduction, which persisted over relatively long periods of block-

ing, were of the order predicted with half of the mixed venous blood flowing through an unventilated area. Similar observations with nitrogen breathing by one lung were made by the same authors and confirmed since by Wright and Woodruff.²⁴ It would seem reasonable to think that if a vaso-motor regulation exists, it should in such an extreme case help shunt a physiologically purposeless blood flow to the contralateral ventilated lung.

Considering all this direct and indirect evidence, we may state that the demonstration of vaso-motor effects in the pulmonary circulation of man is still wanting. At best, it may be conceded that if any vaso-motor activity exists, under normal physiologic conditions, it is superseded by the much more potent mechanical factors regulating pulmonary blood flow. In contradistinction to the systemic circulation, where variations in peripheral resistance serve to regulate flow to various organs according to their needs, all parts of the pulmonary vascular bed and the alveolar spaces are equal in function, hence, there is little cause for a regulating mechanism of blood distribution under normal conditions.¹⁵

It remains to be decided whether the vaso-motor system could serve a useful purpose in regulating the amount of blood stored in the lungs. If it is correct, as I have attempted to show, that the variations in pulmonary circulating blood volume are dependent upon (a) the discharge of both ventricles, (b) the state of distension or retraction of the lung parenchyma, and (c) the intra-alveolar pressure, then vaso-motor regulation is not essential. In cases of emergency such as the early period of exercise, the sudden fall of systemic arterial pressure, caused by vasodilatation in the vascular bed of the muscles, may be prevented by an increased discharge of the left ventricle. The conditions favoring this purposeful increase in pulmonary venous return are thought to be (a) either a preliminary passive congestion of the lung, due to a strong epinephrine-like action on the systemic arterioles, with back pressure effects, during the pre-exercise period of excitation,¹⁴ or else (b) a preliminary active congestion of the lungs, due to deep inspirations, the discharge of the left ventricle being then increased by a forceful expiration as exercise starts.²⁵

If one agrees with Tiemann and Daiber,²⁶ that two types of blood channels exist in the lungs, one with active circulation, the other working as a lock, then vaso-motor regulation becomes indispensable. How-

ever, against the conception of lung blood depot, as postulated by Hochrein²⁵ on the basis of this description, there is, it would seem, lack of anatomic justification. As to the clinching physiologic evidence, which lies in the measurements of sequestered blood, this is, for obvious reasons, still missing.

We shall now turn to the discussion of some observations made during the study of pathological conditions which have an important bearing on the problem of dynamics of the circulation in man.

Clinical investigation of the pulmonary circulation offers an immense field to test physiologic concepts, but methods of study have been until recently inadequate. We shall, here, limit ourselves to the discussion of some problems in which we have been interested:

Mechanism of blood shunting from one part of the lungs to another. Two methods, based on the measurement of respiratory gas exchange may be used in man, to study redistribution of blood, following pneumonia, atelectasis, collapse therapy or partial lung resection, namely (a) the determination in the arterial blood of the oxygen saturation and (b) the simultaneous but separate measurement of each lung's ventilation and gas exchange using the technique of bronchspirometry, which we owe to Jacobaeus, Frenckner and Björkman.²⁷

Reduction in arterial oxygen saturation may be taken to indicate that blood circulates in areas of the lungs improperly or not ventilated. In the absence of a simultaneous measurement of the oxygen saturation of mixed venous blood, the degree of arterial oxygen unsaturation, gives only a qualitatively rough approximation of the proportion of blood circulating through unventilated lung areas. In pneumonia and atelectasis, measurements of the arterial oxygen saturation, show that the blood flow persists for some time in unventilated parts of the lungs. Blood is shunted away from these areas only after the pericapillary pressure, due to exudation, transudation and organization of tissue fluids has increased, diverting blood to other channels through better ventilated areas. As we have shown with H. Maier,²⁸ after lobectomy blood will continue to flow through the poorly ventilated remaining lobe and arterial oxygen saturation may remain low until the latter is again effectively ventilated. In artificial pneumothorax, the arterial oxygen saturation remains normal. According to Hamilton an increased resistance to flow is brought about by the homolateral rise in intrathoracic pressure, and blood flow is redistributed, preferably through the still

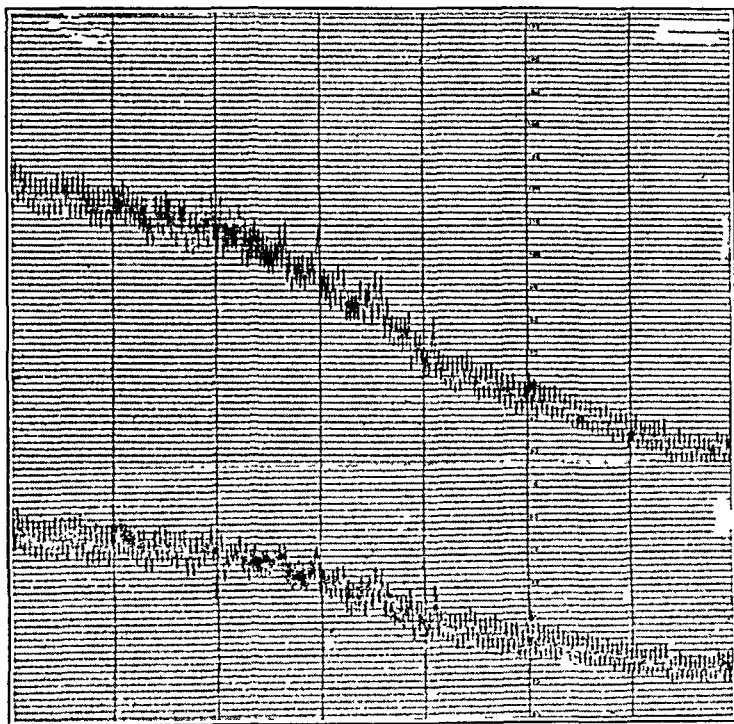


Fig. 9. Simultaneous tracings of ventilation and oxygen intake in each lung separately obtained by the bronchspirometric method. Inspiration upward, expiration downward, oxygen intake of each lung calculated from the slope—vertical lines of the curves at one minute interval—quiet breathing during the first two minutes, leg movements during the next 3 minutes, recovery during the last 2 minutes.

ventilated areas of the collapsed lung and the contralateral lung.

The bronchspirometric method permits a better qualitative estimate of this process of blood redistribution than the measurements of arterial oxygen saturation. The proportional share of each lung in the total oxygen consumption calculated from the slopes of the tracings (Fig. 9) may be taken as a measure of the relative blood flow through each lung, providing the breathing mixture is high in oxygen and the arterial oxygen saturation remains complete. If, in addition, the degree of saturation of the mixed venous blood were estimated directly or indirectly then the absolute values of separate flow could be calculated. In Table II, data on one case with artificial pneumothorax, and one case after lobectomy are presented to illustrate the method. It is seen that in these two patients at rest and during exercise the ventilation and the circulation on the right side were approximately reduced to the same extent.

Very extensive studies having now been carried out in all types of

TABLE II

VENTILATION AND CIRCULATION THROUGH THE RIGHT LUNG AT REST AND DURING EXERCISE IN (a) ONE CASE OF RIGHT ARTIFICIAL PNEUMOTHORAX AND (b) ONE CASE OF RIGHT LOWER LOBE LOBECTOMY

	<i>Rest</i>		<i>Mild</i>
	<i>Normal</i>	<i>Obsv.</i>	<i>Exercise</i> <i>Obsv.</i>
(a) Art. Pnx.			
Right Lung			
Ventilation % of total.....	55	45	45
Circulation % of total.....	55	41	45
(b) Lobectomy			
Right Lung			
Ventilation % of total.....	55	44	39
Circulation % of total.....	55	40	35

surgical disease of the lungs, of therapeutic collapse and pulmonary resection, the following conclusions concerning the problem of blood shunting are tentatively offered in support of the opinion of Hamilton stated above.

Redistribution of blood flow after partial lung collapse and resection depends upon local mechanical conditions. Among these stand out local ventilation, intrathoracic pressures, and local increase in peri-vascular tissue resistance by parenchymatous organization or by complications such as pleurisy and empyema. A small increase in resistance, in one lung, one lobe, or in lobules will cause the blood to be shunted away from the diseased into the intact lung.

Dynamic adaptation to the reduction or the absence of blood flow through one lung. Since it is assumed that the capacity of the pulmonary vascular bed is great, it would appear that its reduction by half and the routing of the entire blood flow through one lung should have little effect upon vascular resistance and; therefore, right intraventricular pressure.

In Table III are tabulated data in 14 subjects with little or no circulation through one lung which indicate that doubling the blood flow through one lung does not increase the intraventricular systolic pres-

TABLE III

RIGHT VENTRICULAR PRESSURES AND BLOOD FLOW IN 3 GROUPS OF PATIENTS (a) AFTER PNEUMONECTOMY (b) WITH FIBROTHORAX (c) WITH THERAPEUTIC PNEUMOTHORAX

<i>Group</i>	<i>No. of Cases</i>	<i>Right Ventricular Pressures</i>	<i>Blood Flow lit/min/m² BS</i>
		Syst/Diast mm Hg	
(a) Post-Pneumectomy	5	30/1	3.3
(b) Fibrothorax	4	27/—1	3.4
(c) Artificial Pneumothorax	5	24/0	4.6

sure. In 5 cases of pneumonectomy, three adults and two children, the average right ventricular pressure measured from 4 to 6 years after the lungs were resected, is, in all but one, at the upper limit of normal. In only one case, that of a man of 69 operated on six years previously for a carcinoma of the bronchus and who had then already a significant degree of bilateral emphysema, was there any evidence of pulmonary hypertension, the right ventricular systolic pressure being 36 mm. Hg. In the 4 other cases, the figures are well within the normal range.

In two children of this group studied with Lester and Riley,²⁹ we measured the maximum oxygen consumption during an exhausting type of exercise and compared them with similar figures in a control group of normal children of the same size and age. In the children with only one lung, the value of maximum oxygen intake, which is related to maximum cardiac output, was identical to the control value. These observations are offered as a further evidence that in subjects with one lung, who were not restrained in their physical activity since pneumonectomy, maximum pulmonary blood flow was not reduced and pulmonary hypertension did not develop after several years. In the four cases of fibrothorax and five of artificial pneumothorax, there was no evidence either of pulmonary vascular hypertension. In one of the cases of fibrothorax, restudied two years later, however, a moderate pulmonary hypertension had developed. The figures are specially significant in the group with artificial pneumothorax, where as a result of the multiplicity of measurement, the figures indicate that the subjects.

were not nearly under basal conditions as shown by the increased blood flow. In spite of this increased blood flow, the ventricular systolic and pulse pressure remained within normal range.

Preservation of normal pressure-flow relationship in patients with only one normally functioning lung may be achieved in two ways which complement each other: (a) an increase in the number of capillaries which are perfused in the remaining lung, (b) an increase in the diameter of the lung capillaries which according to Poiseuille's law could be very small.

Effect of direct communication between the systemic and the lesser circulation. There is another type of pathological condition where a consistent increase in blood flow through the pulmonary circulation may not be associated with pulmonary hypertension, namely the direct shunt of blood from the aorta to the pulmonary artery through a patent ductus arteriosus.

The technique of right heart catheterization lends itself to a physiologic, rational diagnosis of some forms of congenital heart disease. By the use of pressure recordings in and blood sampling from both branches of the pulmonary artery, the right ventricle, and auricle, congenital defects may be recognized in terms of volume of blood shunted and the effects of the abnormal communication upon pressures may be evaluated. Drs. Dexter and Burwell who have made brilliant use of the resources of the technique of catheterization have already studied six cases of patent ductus arteriosus with surgical confirmation and reported to me recently that in all these cases the pulmonary arterial mean pressure was normal, even though in one individual they estimated the shunt through the ductus to be 8 liters per minute.

We have, however, very recently studied in collaboration with Dr. Janet Baldwin, a young girl of three years of age, with a flow of approximately 5 liters through a patent ductus arteriosus, compared to a systemic flow of 2 liters. A marked degree of hypertension in the pulmonary artery had already developed, the pulmonary artery systolic and diastolic pressures being 55/39 with a mean pressure of 46 mm. Hg. or approximately 3 times normal.

There is no doubt that extension of studies of this type will prove of great value not only in the diagnosis but in the comprehension of the physio-pathology of congenital heart defects.

Influence of chronic pulmonary disease upon the development of,

TABLE IV

RIGHT VENTRICULAR PRESSURES, PULMONARY BLOOD FLOW AND LUNG VOLUME MEASUREMENTS IN 17 CASES OF CHRONIC PULMONARY EMPHYSEMA AND FIBROSIS WITHOUT CARDIAC ENLARGEMENT

Group	No. of Cases	Right Ventric. Pressures	Blood Flow lit/min/	Hct. %	Residual Air Total Lung Vol.	
		Syst/Diast mm Hg	m ³ BS		Pred. lit.	Obsv. lit.
A. Emphysema without pulmonary hypertension....	4	24/1	3.0	41	1.3	2.9
					5.3	5.9
B. Emphysema with pulmonary hypertension	4	44/4	3.1	47	1.2	3.6
					5.0	5.6
C. Diffuse fibrosis	9	45/3	3.6	48	1.4	2.2
					5.5	4.2

pulmonary hypertension. The presentation of this problem alone would justify a long discussion. Our concern here is to indicate that an investigative method is available which may help (a) to express somewhat quantitatively the degree of right ventricular strain in chronic pulmonary emphysema and/or fibrosis at a time when radiologic and electrocardiographic data are still equivocal or of no clinical value, (b) to identify the various factors which in these diseases may favor the development of pulmonary hypertension.

In Table IV we have summarized some studies made in collaboration with Drs. Bloomfield, Lauson, Breed and Richards.⁴ We have correlated right ventricular pressure, pulmonary blood flow, hematocrit and lung volume measurements in 17 cases without clinical evidence of cardiac enlargement. The first and second groups comprise cases of chronic pulmonary emphysema without and with pulmonary hypertension, the third, cases of chronic pulmonary fibrosis complicated with emphysema. The data are remarkable in showing (a) that pulmonary hypertension had not developed in cases with moderate degree of emphysema, (b) but that in the group with the most marked degree of emphysema, hypertension in the lesser circulation was present, and finally, (c) that in the group with fibrosis and moderate emphysema and apparently small heart, pulmonary hypertension was already quite marked. For a

time, it was our impression that polycythemia played a decisive role in the early development of pulmonary hypertension, by increasing the resistance to flow. However, a breaking down of the hematocrit figures in the two groups of emphysema with and without hypertension, does not at present seem to lend support to this hypothesis.

Many factors are responsible for the increased resistance to flow in pulmonary emphysema and fibrosis. With adequate physiologic methods it should be possible to correlate some of the data as we have attempted in this limited series. In the future it will be of interest to the clinician that figures of pressures in the right ventricle and pulmonary artery be correlated with signs usually interpreted as indicating pulmonary hypertension and with studies of electrocardiograms, using the most recent methods for the detection of early right ventricular strain.

In this presentation, I have omitted discussing many problems of interest to the clinician. However, I shall have fulfilled my purpose if I provided adequate support to the following conclusions:

(1) The volume of blood contained in the pulmonary vessels is governed by the relative discharge of the two sides of the heart which are under the control of the dynamic changes in the systemic circulation.

(2) The capacity and the flexibility of the small vessels in the lungs are such that a several fold increase in blood flow may be accommodated with negligible pressure changes, a remarkable example of purposeful adaptation to function.

(3) Under variable physiologic conditions a clear cut demonstration of vaso-motor activity in the pulmonary vascular bed is still lacking.

(4) Sound physiologic methods for the study of the pulmonary circulation are now at the disposal of the clinical investigator and may be used for diagnostic purposes in well chosen cases of congenital cardiac malformation.

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CURARE AND INTENSIVE PHYSICAL THERAPY IN THE TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS*

NICHOLAS S. RANSOHOFF

INTRODUCTION

A METHOD of treatment of acute anterior poliomyelitis has been developed at the Monmouth Memorial Hospital in Long Branch, New Jersey, which utilizes the relaxing effect of curare and intensive physical therapy from the onset of the disease. Every attempt is made to reestablish and maintain normal muscle physiology. In as much as any loss of normal muscle length is accompanied by loss of muscle strength, the full physiological power of the muscle is sought and developed.

Twenty-nine patients were treated in 1945 and, at the present time, there are twenty-one patients who are completely well. There are three patients who have paresis of one or more muscle groups. There are four patients who have paralysis of either a major muscle or an extremity. There are no residual abdominal or back muscle weaknesses. There was a single fatality due, in part, to the mechanical failure of the respirator.

Electromyography: Electromyographic studies were performed on all the patients admitted to the hospital with acute anterior poliomyelitis. The following observations were made:

1. There are resting action currents present in the muscles of patients with acute anterior poliomyelitis.
2. The resting action currents are diminished or obliterated by means of curare and intensive physical therapy in the form of stretching beyond the point of pain.
3. Sherrington's law of reciprocal innervation is interfered with in patients with acute anterior poliomyelitis, so that the antagonists may be more active than the agonists.
4. The administration of curare assists in the reestablishment of the physiological phenomenon, reciprocal innervation.

* Presented before the Section of Orthopedic Surgery of The New York Academy of Medicine, November 15, 1946.

5. On voluntary contraction, a poliomyelitic muscle varies from the relatively normal in both potential and frequency.

6. The pathological stretch reflex is present in patients with acute anterior poliomyelitis. This is decreased or eliminated by the administration of curare.

Dosage: The dosage of curare which is used is 0.9 unit per kilogram of body weight every eight hours for the first twenty-four hours. This is always administered after meals. The preparation of curare which is used is Intocostin (Squibb). It is administered by intramuscular injection. After the first twenty-four hours, the dosage is increased to 1.5 units per kilogram of body weight if there has been no adverse reaction. Over five thousand injections of Intocostin have been given in 1945 and 1946 to patients with acute anterior poliomyelitis. Physostigmine, the pharmacological antidote for curare, has been administered only once and, whether or not that was necessary, is still a moot question. The policy has been established at the hospital that if there is doubt in anyone's mind, the physostigmine, which is always ready, is given.

Therapeutic Effects: The following therapeutic effects have been obtained:

1. Blurring of vision or diplopia. These are the symptoms indicative of adequate dosage.

2. Relief of pain.

3. Sufficient relaxation of muscles which have been in spasm to allow intensive stretching procedures.

4. Temporary exaggeration of muscle weaknesses present, enabling early discernment of minor weaknesses undetectable before curarization.

Physical Therapy and Occupational Therapy: The physical therapy procedures which have been adopted are designed to reestablish normal, or as near normal, muscle physiology as possible. It is freely admitted that there can be no possible effect of the method of treatment on spinal cord pathology. It is maintained that the best possible results will be obtained with whatever muscle power can be salvaged by the following procedures in conjunction with the administration of curare.

Curare without physical therapy or physical therapy without curare will not give the desired results. This cannot be emphasized too forcibly. Muscle lengths are maintained by intelligent stretching. This stretching must be carried beyond the point of pain. It is best done by carrying the part to the point of pain and then, with gentle pumping movements,

increase the range of motion. Then rest and repeat. With each repetition, a greater range of motion will be obtained. Care and patience are imperative in these manipulations.

Exercises are designed primarily to develop and improve coordination and flexibility. That the muscles are strengthened through these exercises is coincidental. It is not implied that individual muscle group exercises are never given. They are. But the majority of the exercises are so designed that the part as a whole is the point of focus rather than an individual muscle.

Occupational therapy plays an important part in this regimen of treatment.

Psychological Approach: The confidence and cooperation of the patients must be obtained by the physical and occupational therapists. Every possible device must be used to keep the patients' morale at a high level. Certain standards of behavior in treating patients with acute anterior poliomyelitis have been established at the Monmouth Memorial Hospital. These are, in brief, as follows:

1. Never lie to a patient. If the patient is going to be hurt, tell him so.
2. Never bribe a patient in an endeavor to get his cooperation.
3. Make it a practice to spend some time in recreation with the patients daily. This may consist of roughhouse, reading, or innumerable methods of having the patients do things under the guise of play. This is essential so that the physical therapist does not become an ogre, but maintains a normal personal relationship with the patient. This is just as important for the adults as for the children. It is a *real* program based on elementary psychological principles.

SUMMARY

1. A method of treatment of acute anterior poliomyelitis has been presented which utilizes the relaxing effect of curare to enable the immediate institution of intensive physical therapy, thus reestablishing and maintaining normal muscle physiology.

2. Electromyographic studies were made on each of the twenty-nine patients with acute anterior poliomyelitis treated by the described method in 1945.

3. The dosage of curare recommended is 0.9 unit per kilogram of body weight every eight hours for the first twenty-four hours. It is then

increased to 1.5 units per kilogram of body weight if there has been no adverse reaction.

4. The physical and occupational therapy procedures which are used are based on the objective of reestablishing and maintaining normal muscle lengths. Patients are made ambulatory as soon as possible, thus preventing loss of the kinesthetic sense of the upright position.

5. The psychological approach of the physical and occupational therapists to the patients is considered to be of great importance.

CONCLUSIONS

1. It is believed that the described method of treatment of patients with acute anterior poliomyelitis will accomplish the following: (a) Shorten the period of hospitalization. (b) Decrease the number of personnel necessary to care for the patients. (c) Give better functional results.

2. No claim is made that this is a cure for acute anterior poliomyelitis but that it is a better method of treatment.

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



FEBRUARY 1947

THE CENTENNIAL CELEBRATION
OF THE ACADEMY

GEORGE BAEHR

President, The New York Academy of Medicine

I N this, the one hundredth year since the founding of the Academy, it is the solemn duty of its officers and of all devoted Fellows to review the history of the institution which we have inherited from our predecessors, so that we may renew our faith in its important mission and look forward with hope and confidence to the years of public service which lie ahead. Although its beginning was most humble, a room over a coal yard at 175 Wooster Street with the imposing name, Convention Hall, the spirit of the enthusiastic Founders of the Academy was high and noble. They dedicated themselves to the establishment of an institution for the improvement of medical education, the advancement of the public health, the elimination of quackery and malpractice and the instruction of the public on matters of health and hygiene. In spite of the primitive state of medicine in the year 1847, the magnificence of the spirit which moved the 185 Founders and the appeal which their high motives made to the medical profession and to the general public in that year can be judged from the fact that the First Anniversary

* Inaugural Address delivered at the Stated Meeting of the Academy on Thursday, January 2, 1947.

Oration which was delivered in the Broadway Tabernacle by Dr. John W. Francis, second President of the Academy, on November 10, 1847, attracted an audience of more than 2500 persons. This may well be regarded as the Academy's first and most popular Lecture to the Laity.

At the first meeting of the Academy on January 6, 1847, the library was started with a gift by Dr. Isaac Wood of three volumes of Paine's Commentaries. From this small start, and in spite of many decades of discouragingly slow progress, the goal was reached within our generation, so that we find ourselves today in the possession of one of the great medical libraries of the world, housed in one of the most beautiful and impressive buildings in New York, with its commodious meeting halls and conference rooms. In this modern home the scope and importance of the Academy's daily work for the advancement of public health, medical education and public instruction far exceed the most ambitious dreams of the Founders.

The Academy's Centennial Celebration will open on the sixth of March, with an assembly of the Fellowship and the friends of the Academy. As we do not have a hall in the Academy building large enough to hold the entire Fellowship, we have engaged the grand ball-room of the Waldorf-Astoria for that evening. I am privileged to announce that The Centennial Discourse will be delivered on that occasion by Professor John A. Ryle, formerly Regius Professor of Medicine at Cambridge, England, and now head of the Institute of Social Medicine at Oxford. His address will be on "Social Pathology and the New Era in Medicine."

We owe the rare opportunity of his visit to the Academy on this historic occasion to the kind assistance of the Rockefeller Foundation.

Following the opening dinner meeting of the Fellowship, we have planned a series of activities in the Academy building which will continue daily throughout the months of March and April. Each of the eleven Sections of the Academy will celebrate the Centennial with a dinner of its own members followed by a memorable meeting in which eminent authorities in the specialty from New York and other parts of the country or from abroad will participate. Each of the Academy's Standing Committees has arranged for a three day Institute or round table conference devoted to Post Graduate Medical Education, Public Health, Social Medicine, Hospitals, and Medical Libraries. In addition to Fellows and invited guests, representatives of the medical schools and

of governmental and voluntary agencies in each of these fields will participate.

Various affiliated clinical and scientific societies such as the Harvey Society, the Society for Experimental Biology and Medicine, New York Heart Association, New York Diabetes Association, New York Roentgen Society and others are planning to hold special meetings during March and April in the Academy to commemorate the Centennial. The Academy has also offered its hospitality to other sister academies and societies in this area such as the New York Academy of Sciences and the New York Chapter of the American Chemical Society.

An historical exhibit of the Academy and its role in medical progress over these one hundred years is being assembled, which will be on view in the Academy throughout March and April. Among other historical material of rare interest, it will include the portraits of the thirty-nine past presidents and many other distinguished Fellows who contributed to the advancement of the medical sciences during the past century.

With the help of the City Planning Commission, the Department of Hospitals, the United Hospital Fund and the Hospital Council of Greater New York, an exhibit is also being assembled dealing with the history of the older Municipal and voluntary hospitals of the City, at which plans for their post war development will be shown. At this exhibit on hospitals, a master plan for the future hospital development of Greater New York will be revealed to the medical profession and to the public for the first time.

Meanwhile, throughout the City, the Academy's Centennial will be celebrated by special public exhibits on medical and historical subjects at the Metropolitan Museum of Art, the New York Public Library, the New York Historical Society, the Museum of the City of New York and at private art galleries which possess famous prints collections and other memorabilia on the medicine of a hundred years ago. As a special feature of the celebration, your president will broadcast over a nationwide hook-up an address on "A Hundred Years of Medical Progress."

The Academy's special Committee on Medicine and the Changing Order has planned a three day symposium on Social Medicine and the related changes in medical practice and medical education which will be necessary to make the full benefits of modern preventive and curative

medicine available to all people. The occasion will also be utilized to make public announcement of the release and publication of this important Committee's complete report and recommendations which, it is hoped, will have an important influence upon future changes in the methods of medical practice and medical education in this country.

I cannot close this brief forecast of the events of the Centennial year without mentioning the publication by the Committee on Medicine and the Changing Order within the last two years of ten monographs covering almost all the present day problems concerned with medical care, from Hospitals and Nursing to Medical Insurance and Medical Education. The monumental labors of this distinguished Committee for almost four years under the untiring leadership of its Chairman, Dr. Malcolm Goodridge, and of its Secretary, Dr. Iago Galdston, will culminate in the publication in March of the volume embodying its Report and Recommendations. I must here record our indebtedness to the Commonwealth Fund, the Josiah Macy Jr. Foundation and the Milbank Memorial Fund for the financial support of this most important undertaking in the history of the Academy. I recommend the Final Report to you for careful reading.

Finally, I am pleased to announce that the compilation of a comprehensive History of The New York Academy of Medicine, which Dr. Philip Van Ingen generously undertook almost two years ago, is approaching completion. This interesting volume will be ready for publication and distribution during this Centennial year.

In all the commemorative exercises of the Centennial, the major theme will be the relation of modern medicine and its various clinical and scientific branches to the changing social order of today. The celebration will be founded on the premise that the accomplishments of the past cannot be accepted as virtues except as they may be used as a background upon which to build a new pattern of future service to the medical profession and to the people of this City and of the Nation.

By the time the celebration is ended, the Fellowship and the public will have been made fully aware of the role which the Academy has played in the life of this City and of the Nation over the last hundred years, and of its potentialities for continued service to the people and to the medical profession. The Fellows of the Academy have assumed the burden of a great responsibility. I take this occasion to appeal to the general Fellowship for help with the labors which lie ahead. We also

need your assistance and that of your lay friends and patients in carrying the financial load which our library and the work in the various fields of public service entail. Knowing our history, you can point with satisfaction to masterly accomplishments of the Academy in the reduction of maternal deaths, the establishment of a national quarantine service, the sanitation of cities, the abolition of the obsolete coroner system, the establishment and improvement of vital statistics, the development of a Standard Nomenclature of Disease that is now used in almost every medical school and hospital throughout the United States and to many other public services too numerous to mention.

As with all institutions at this time, salaries have climbed and costs of all kinds have mounted well beyond our present income, so that the past year has ended with a deficit of \$40,000. We have reluctantly raised our dues for 1947 25 per cent, but I would have you remember that the dues from Fellows and library subscribers make up less than one-fifth of our expenditures. The other four-fifths must come from income on the endowments and bequests which the fellows and friends of the Academy have contributed in the past. The Academy needs an additional income of \$50,000 in 1947 and an increase in its endowment of \$1,000,000. Let each of us ask himself the question, "What can I or my friends do for the Academy either in direct services or in some measure of financial assistance?" The shelves of our library stock rooms are a solid mass of books, in many places two rows deep, so that the library attendants, with the best of good will, can no longer serve you as promptly as they did in the past.

I am greatly honored to be reelected as your President for another two years, and shall do my utmost to deserve your confidence.

In September, Dr. Herbert Wilcox retired from the Directorship after having served the Academy devotedly and most efficiently since April 1939. We shall long miss his kind help and his patient leadership. Upon his retirement, Dr. Howard Craig took over the administrative responsibilities of the Academy. Under his resourceful direction and with your help, the Academy will carry on in the tradition of the last one hundred years.

THE ACADEMY CENTENNIAL

HOWARD R. CRAIG

Director, The New York Academy of Medicine

THE first hundred years of any institution, such as The New York Academy of Medicine, may well be, as the saying goes, the hardest. The completion of that century, covering its metaphorical weaning, toddling and adolescence, may be the product of mere survival, or it may be the result of a vital, purposeful career. The late Dr. William W. Herrick in his Presidential Address of 1945 stated that any institution was but the lengthened shadow of a man. Little did Stearns, Mott, Purple, Francis, Janeway, Delafield, Jacoby and the others realize the length or the substance of their shadows, for they builded solidly on service to the ill, to their confrères, and to the public well-being.

During the Centennial Celebration of The New York Academy of Medicine in March and April, 1947, this note of historical retrospection will be amplified and developed in the forthcoming History of the Academy which is nearing completion; in the Section meetings; and in exhibits both at the Academy and at various coöperating institutions scattered over the City.

The present activities and functions of the Academy through its Library, its Sections, and its Standing Committees on Medical Education, Medical Information and Public Health Relations, are common knowledge though sometimes not as thoroughly appreciated by the Fellows as by physicians in other cities and states.

The Institutes sponsored by the Committees on Library, Public Health Relations, Medical Education and Social Medicine, will be in the nature of three day round-table working conferences arranged particularly for workers and other persons interested in those particular fields. The subject matter and dates for these Institutes have already been announced and the names of the discussion leaders will be forthcoming shortly.

Invitations for the Centennial Celebration Dinner on March 6, 1947 at the Waldorf-Astoria Hotel has been mailed to the Fellows. Each Fellow is urged to make his reservations as early as possible.

RECENT ADVANCES IN
CANCER RESEARCH**The Ludwig Kast Lecture*

PEYTON ROUS

The Rockefeller Institute for Medical Research

I N 1913 H. G. Wells remarked, in *The New Machiavelli*, that to organize a laboratory expressly for cancer research was like issuing a license for a bath chair to scale the Himalaya Mountains. Yet already several such licenses had been issued; the laboratories were working valiantly; and now in 1946 the bath chairs are far up the slope of the mountains, and all about them, some in front, some behind, are other motley vehicles, not to speak of solitary climbers legging it along. The present is a good moment to speak of advances made.

Experimental cancer research is less than 50 years old, even younger than bacteriology; a few of the men who began it are still active. It got off to a start when the rewards of the close observational study of human cancer had become small. Then for the first time medical scientists paid attention to the fact that animals have tumors too—a fact previously known for some while. With the demonstration that these growths are true neoplasms and the maintenance of a few by transplantation, things got under way. At first hopes ran high that the cause of cancer would be found soon, but then it became clear that the transplanted tumors carried the secret along with them in host after host. Nothing could be procured from the tumor cells that would cause other growths, and anything killing them, in even the least disturbing of ways, brought the neoplastic process to an end. Furthermore, the transplanted tumors failed to call forth any resistance on which attempts at cure could be based in the human being; the new hosts reacted to the grafts merely as composed of tissue foreign to their bodies, not as tumor tissue. The cultivation of cancer cells *in vitro*, though occupying many workers, contributed no deep-going enlightenment, and until 1915, when tumors were purposely

* Presented at the 19th Graduate Fortnight of The New York Academy of Medicine, October 7, 1946.
From the Laboratories of The Rockefeller Institute for Medical Research, New York.

induced by means of tar, workers were unable to get at the conditions determining the occurrence of neoplasms. Until then, observations on the "precancerous states" of man had been the sole reliance of the investigator, since the spontaneous growths of animals had been too far along when first encountered to be informing. But now at last the conditions leading to cancer could be got at experimentally.

What are the recent advances? It will doubtless be agreed that when a fact or idea first attains recognition by scientists, this constitutes a recent advance though it may have been decades in the making. Perhaps the largest step forward of the last few years has been the very gradual comprehension, gained incidentally to the experimental production of tumors, that cancer is not a separate neoplastic entity, does not stand off by itself, but is merely one amongst the immense group of the true neoplasms, all these being expressions of a single general principle, the neoplastic principle as one might call it, however widely they differ in cellular make-up. To the practitioner this may seem an academic ruling; he knows but too well that every sort of tumor has its special characters, and even each growth an individuality of its own. For him the neoplasms cannot but be heterogenous diseases, and for the safety of his patients he must continue to look upon them as such. Until a little while ago experimenters did so too, and indeed when they first found themselves able to produce tumors they concentrated on getting cancers for study, disregarding almost entirely such other growths as happened to be elicited; they even applied the term "carcinogenic" to the agents which induce tumors, as if these gave rise to malignant epithelial tumors and no others—a usage which persists to this day. Now every investigator realizes that these agents call forth not only cancers but growths of all the main categories dealt with in the textbooks on human neoplasms. A single chemical carcinogen may elicit the whole diverse array, the precise kind of tumor which appears in a given experiment depending upon the kind of cells on which the agent is brought to bear. Not only this, but they call forth the leukemias as well, and almost insensibly these latter have come to be acknowledged as within the neoplastic fold. Every now and then leukemias have been encountered in animals, or elicited, consisting of cells which give rise to tumors if injected into the connective tissue instead of into the blood. The investigator who tackles the cancer problem really tackles the tumor problem as a whole, and he can hope by studying one growth to learn something

about those of many sorts. From here on, in the course of this survey, the terms "cancer" and "tumor" will often be used interchangeably.

Long before the first neoplasm was induced in an animal physicians had good reason to be aware that there are agents in man's environment which cause him to have tumors. But nobody had any conception of how widely distributed these agents are, or of how insidiously they work in some instances, or what a great host of them there can be—for chemists are now synthesizing new ones all the time to learn how they act, and more will be encountered as unforeseen hazards of new industrial processes. In the last few years we have come to know them in bewildering variety. We literally spend our lives amidst them; the very sunlight gives rise to cancer, and the only reason any of us go free from the disease is because the action of most carcinogens is occasional or weak.

Two British workers, the Kennaways, have found on scrutinizing English statistics that cancers of the skin, mouth, throat, esophagus, and stomach, all the way to the pylorus, are more frequent the lower the social scale of the human individual. Evidently the skin of poor people is more liable to be injured in ways that bring on cancer than of people in easy circumstances, and what they eat and drink is in all probability more likely to contain carcinogens. The thought that we may take in such substances with our food is disturbing. Recently it has been discovered that rats fed 2-acetaminofluorene develop tumors after a while, here, there or yonder, at spots far distant from the digestive tract, and some of the azo dyes have proved capable of giving rise to cancers of the liver when they are fed to rats placed on special diets. One such substance has been used in the past to color butter. They are harmless when given with certain food stuffs, and many workers attach great significance to this fact, though others discount it, pointing out that the dyes cannot make the liver cancerous unless they reach this organ, and that they become so strongly adsorbed to certain food stuffs as to be carried intact through the intestine, while in other instances they are degraded and rendered harmless by the bacterial flora of the gut, a flora which differs with the character of its contents. However all this may be, the findings to the present, and the fact that certain hydrocarbons are carcinogenic, have together suggested the possibility that the eating of superheated fats, such as may be formed when frying is bungled, may be responsible, at least in part, for gastric cancer. The evidence

on this point is still equivocal, despite much experimentation.

A far more difficult problem than the carcinogens round about us—since these can be warded off in proportion as we perceive them—is that of carcinogenic agents arising within the body. There are reasons to suppose that they often do so. Some years ago the fact was brought out that tar produced by heating human skin may induce skin cancers when painted on the backs of mice. Of course this does not justify the conclusion that the skin elaborates tar under natural conditions: one might almost as easily suppose that because the body contains hydrogen, oxygen, and nitrogen, it produces fuming nitric acid. But gradually, as new hydrocarbons capable of inducing tumors have been synthesized, it has become plain that some of them are nearly related chemically to substances normally present in the organism, methylcholanthrene for example, almost the most powerful of chemical carcinogens, having a close structural relationship to cholic acid. Also in the last few years the discovery has been made that extracts of some diseased human tissues are capable of producing tumors in animals. The Negro miners of the Bantu race in the Witwatersrand of South Africa nearly all have abnormal livers; hepatic cancers are frequent amongst them; and extracts of their livers are capable of causing sarcomas when injected into the subcutaneous tissue of mice, and of evoking both papillomas and epidermoid cancers when painted on the skin. It might be argued that the chemical procedures employed in obtaining the extracts have resulted in the production of substances not existing naturally; but control extracts made in the same way from the normal livers of Europeans have a carcinogenic action less frequently. Furthermore, Schabad, who did the first experiments of the sort described, produced sarcomas in mice by the injection of mere benzene extracts of cancerous human livers. The fact that some extracts of normal livers have a similar effect does not lessen the significance of Schabad's finding; for, as already stated, it is not the presence of a carcinogen but its presence in effective quantity which determines whether a tumor will arise. The recognition of endogeneous agents and conditions, developing within the organism and capable of causing tumors, is one of the pressing tasks of the day.

For some years it has been known that certain normal substances, namely hormones, may give rise to tumors when they act too forcefully, as when they are injected in quantity over long periods of time. They are not true carcinogens themselves, but are indirect in their influence,

bringing about such pathological states in the tissues they affect, getting the cells into such a disordered condition, that some of them undergo neoplastic changes after a while for reasons unknown. Repeated injection into mice or rats of the estrogens, for example, may render the tissue of the mammary glands so abnormal that cancers eventually take origin from it, and not only may such growths be thus produced but uterine carcinomas also, and lymphosarcomas, leukemias, testicular and pituitary neoplasms and bone tumors. It has become plain of late that most of the hormones influence other organs in addition to those to which they are obviously dedicated, and nobody knows to what kinds of tumors they may not give rise next if administered in sufficient quantity.

There is an obverse to these findings. Reducing the action of hormones may mean the prevention of certain tumors. It seems possible that enough estrogens may be elaborated within the bodies of some supposedly normal women to bring about the mammary disturbances out of which cancers come. If this is the case steps can be taken to lessen or combat the influence of these substances and the growths thus be ward off.

For nearly 75 years doctors have been aware that many cancers arise where there is chronic disturbance of the tissues, at flexures of the intestine for example, and now the accumulated evidence warrants the conclusion that this is the rule for tumors in general, that they appear only where pathological changes have taken place. Yet mere chronic inflammation is not enough in itself to cause growths; if that were the case, epidermoid carcinomas would arise wherever lupus existed, and cancer would follow upon every leg ulcer present for years. Some special factor there is which precipitates the neoplastic change. Ordinary histological techniques have failed to disclose its character; they are bankrupt in this connection. But of late, new methods have been devised, notably that of Caspersson, a Swedish worker. He has utilized ultraviolet rays of special wavelengths to take photographs of microscopic sections of tissue, and has thus obtained detailed pictures which tell large new facts about the happenings in cells.

At the time when neoplastic changes first appear in response to a carcinogenic agent the tissue acted upon is in a hyperplastic state. But often the hyperplasia is secondary to injury—as for instance in skin injured with Roentgen rays; and certain workers, notably Haddow of the Royal Cancer Hospital in London, have concluded that the cells

become neoplastic while they are faring badly and that the chemical carcinogens act through the depression of cellular activities that they bring about. The injection into animals of some of these substances causes transplanted tumors to grow more slowly, and knowing this fact a European surgeon, just before the War, actually painted operable human cancers of the skin with a powerful carcinogenic hydrocarbon, ignoring the danger that other growths might arise later on as a result of its action. He reported that the tumors disappeared, and in the present state of Europe the end-results of the treatment may never be known. Haddow himself has synthesized numerous hydrocarbons nearly related chemically to those of carcinogenic sort, hoping to obtain some which would check established tumors while giving rise to none on their own account. His results in animals encourage further work and he has now begun clinical trials on inoperable cases. Laboratory observations made in our own country during the War on the effects of the nitrogen mustards to retard cell activity have led to the utilization of such substances in the treatment of lymphoid tumors and leukemia in human beings. There cannot be too many well-reasoned efforts such as these.

What can the cause of tumors be, the actuating cause which keeps them going? One favorite idea went out the window during the first years of experimentation with carcinogenic agents, the idea that cells run amuck and form tumors because of a relaxation of some governing influence exerted by the organism, which had kept them in order previously and all doing what they should. On painting the skin of an animal at different places successively with a chemical carcinogen, it has been found no easier to induce a second tumor, or a third or a fourth, than the one which had arisen at the spot painted first; if the body really exercises a control this is as tight as ever. The conclusion, that tumor cells are not mere ordinary cells which have seized an opportunity to go on the loose, but differ from them in some distinctive way—a way yet to be ascertained—underlies all the present-day searchings for chemical traits peculiar to cells in the neoplastic state. The hope that they may elaborate some specific antigenic substance and thus provide a serological test for the presence of a neoplasm goes back to the first years of immunology. Very recently a distinctive antigenic substance has been demonstrated to exist in the Brown-Pearce rabbit carcinoma; but further work has shown it to be peculiar to this neoplasm, quite different serologically from another antigen encountered in a

second kind of epidermoid carcinoma of the rabbit. On the basis of these findings one might perhaps look forward to a galaxy of blood tests, each for some tumor of special sort, but not to a single test which would help in the generality of human instances, those in which the doctor wants to know whether there is any tumor at all in his patient, its precise nature coming afterwards. And even the possibility of special tests is problematic, since in rabbits carrying the tumors above mentioned the antibody formation essential to a serological reaction often fails to take place, although the tumors themselves regularly contain the specific antigen.

Most of the agents which are effective in producing tumors, the Roentgen ray and *Bilharzia* ova, to cite extreme examples, cannot possibly be the actuating causes of the growths. Their part is played when they have produced neoplastic change; the tumor flourishes on its own, just as a fire does which has been kindled in any one of a myriad ways. But the fact that certain hydrocarbons have proved capable of inducing tumors has led investigators to ask whether substances having similar effects may not be continually formed within cells after these become neoplastic, and maintain them in their abnormal state. Even if this is not the case a knowledge of precisely what the synthetic carcinogens do should prove broadly enlightening. Gifted chemists are now concerned with these possibilities, trying to learn whether there is not some radical or bond or configuration common to carcinogenic molecules which is responsible for their singular effect on the cell. The most widely different carcinogens may give rise to growths of identical sort.

Large opportunities for studies on tumor causation have been provided of late through a feat of the geneticists. By mating mice, brother to sister, year after year, for as many as fifty generations they have untangled the hereditary traits which exist interwoven in the ordinary animal. They are now in possession of breeds of mice consisting of individuals which are not only homogeneous, in that their normal tissues, and their tumors as well, can be transplanted from one to another as successfully as if transferred within the same organism, but which exhibit special characters that are ordinarily obscured by a mixed inheritance and hence find expression only now and then. Some of the pure-bred strains of mice have striking liabilities to spontaneous tumors of one sort or another, while others have equally remarkable freedoms from these growths. Nearly every animal of certain breeds may develop

lung tumors, or liver tumors, or leukemia, or every ageing female may have mammary cancer, whereas in other strains such neoplasms never appear. And back of the primary tumor liabilities there may be secondary ones; an animal escaping the mammary carcinoma which kills most individuals of its strain may in all likelihood die of leukemia later.

What are the reasons for these differences? At first it was supposed that the various tendencies to tumors are hereditary, passed on through the chromosomes. For most of them this may indeed be true. But a worker in Holland and others at Bar Harbor, Maine, who studied crosses between mice of strains having marked and slight liabilities respectively to mammary cancer, found simultaneously that the tendency to such tumors is handed down through the mother. There followed startling discoveries by Bittner, one of the Bar Harbor group. He took young mice of strains highly liable to mammary cancer away from their mothers as soon as they were born; had them suckled by females of a strain with no such liability; and found that thus they were rescued from having mammary cancer in later life. By carrying out the experiment in the opposite direction the tendency to mammary cancer was conferred upon breeds not having it ordinarily. The tendency is passed along from one generation to the next by something in the mother's milk, the "milk factor" as it is now called. A single nursing just after birth is enough not only to establish the factor in the young female itself but in its descendants as well. And most important, whole races of mice can be rescued from having mammary cancer by preventing the milk factor from reaching the original mother of the race.

The factor does not produce its effect at once. It somehow reaches the mammary tissue from the gut, increases in quantity as the glands develop, and when the mouse grows old, one adenocarcinoma or several make their appearance in the breast tissue. This happens in practically every individual of some breeds. Yet nothing can be got from the mammary glands, or from the cancers, which will cause tumors directly on injection into other ageing individuals, only the milk factor, though this in great amount. Titrations have shown that one-millionth of a gram of mammary tissue yields enough of it, on extraction with salt solution, to confer the tendency to mammary cancer on an endless series of animals. A great deal has been found out about the factor in recent years and everything, its size, its physical character, its antigenicity, its continual increase in association with living tissue, its

infectivity—for it sets up what must be regarded as a postnatal infection—all puts it in the category of the viruses save the fact that it does not induce disease directly. The most reasonable explanation for the way it works is that it is a harmless virus, thriving and increasing in the mammary tissue, and varying to become a tumor-producing virus when its cellular environment undergoes pathological alteration, as in the breasts of female mice which have grown old.

These discoveries have caused many surmises as concerns human cancers of the breast. One cannot doubt that within the human species there are hidden liabilities to tumors which find individual expression now and again, but statistics show that only very rarely is the layman's fear justified that there is "cancer in the family." Perhaps, on the analogy of inbred, pure-strain mice, brother to sister matings of human beings during a thousand years might bring out pronounced familial differences as concerns the incidence of tumors; but we can be thankful that, as matters stand, we are a mixed lot. A few workers with the milk factor have lately urged that new-born babies of human families in which mammary cancer has occurred should be taken away from their mothers before they have nursed at all, and be raised on the bottle; but this would be to subject such children to very real dangers because of fears that are ill-grounded in the generality of instances, as the statistical evidence proves.

A great deal of experimentation has been done to learn whether other tumor liabilities in mice besides the mammary are transferred through the milk, but the results have been negative save perhaps in the case of certain leukemias.

The existence of the milk factor has brought new support to the conception that tumors in general may be due to viruses. As is well known, many of the neoplasms occurring spontaneously in chickens yield such agents, with which growths of identical sorts can be produced. Most of the theoretical objections to viruses as the general cause for tumors have been done away with by this finding, but it has not lessened the practical ones. Despite persistent efforts during the last thirty years no viruses capable of directly causing neoplasms have been procured from rat or mouse tumors—the common currency of the laboratory—though a few out-of-the-way growths have yielded them. Lucké has demonstrated that an adenocarcinoma of the kidney which occurs often in the leopard frogs of American swamps is due to a virus,

and the huge papillomatous growths frequently present on the skin of Western cottontail rabbits are also virus-induced, as Shope showed. The papillomas behave like true tumors at the brink of malignancy, and after they have grown for some months metastasizing squamous cell carcinomas often arise from them by secondary changes in their virus-infected cells. These cancers would never happen were it not for the action of the virus, and they appear so soon that the latter rates as the most powerful of known carcinogens for the rabbit. Yet nothing can be extracted from the cancers that will cause such growths, or even papillomas in other individuals; and it is possible that the virus does no more than start off a process with which, like the ordinary physical and chemical carcinogens, it has nothing further to do. The great majority of workers at the cancer problem see little in the idea that the generality of tumors are due to viruses, and recent experimental evidence, into which there is not time to go, speaks against the assumption that agents of this sort, passing from one individual to another, can be their cause. But decisive evidence in the matter may be available soon, for much can be expected of the new techniques for visibility now under development. Already Claude and Porter have obtained pictures of chicken tumor viruses within the cells of the sarcomas they induce, being enabled to do this because the cells spread out so thin in tissue culture as to permit photography with the electron microscope. In a few years at most it should be possible to search the cells of mammalian growths with the same instrument.

One might think that pathologists would now be possessed of a thorough knowledge of the natural history of tumors as result of the diligent observations made on human growths during the last hundred years; but the very definition of a tumor misses the mark, as proven by recent discoveries. The conception has long been axiomatic that a tumor is an autonomous new growth. But Huggins' demonstration that many prostatic cancers, including some which have metastasized, stand still for years or disappear after removal of the patients' testicles shows that even the cells of malignant growths, of cancers ordinarily fatal, are not always truly independent in their behavior. The cells of the prostatic cancers which behave in this way have been spurred on by the male sex hormone elaborated within the gonads and responsible for the normal activities of the prostatic epithelium. When, after orchidectomy, they are no longer thus urged, they cease to proliferate and some-

times they are actually incapable of maintaining themselves. By combatting the influence of testosterone with natural or synthetic estrogens similar results have been obtained.

The significance of this discovery far transcends its practical application; for it means that thought and endeavor in cancer research have been misdirected in consequence of the belief that tumor cells are anarchic. As every medical student knows, the extent to which these cells deviate from the normal varies from tumor to tumor over a wide range, and the greater the divergence the more likely is the growth to be malignant, by and large. It has been known too that the cells of nearly all cancers make some attempt at the customary tasks of normal elements of the same sort, perhaps forming gland-like structures, or making more or less successful attempts to differentiate like the stratified squamous epithelium from which they derived. But no one had realized that neoplastic cells making such attempts at differentiation might also respond in line of duty to normal physiological influences such as the hormones exert. How widely this principle finds expression in the behavior of tumors has yet to be learnt, and how successfully it can be utilized in repressing them. The course of events with prostatic cancer has seemed to justify the expectation that many mammary cancers would dwindle when the influence of the female sex hormone was lessened by removal of the ovaries or by injections of testosterone. The results with women have not been very promising thus far, but the paradoxical fact that cancers of the male breast yield to orchidectomy, or to stilbestrol, is encouraging; for it makes sharply plain the existence of critical factors which have yet to be understood and pressed into service.

A priori one might suppose that the prostatic cancers composed of cells which have lost all the morphological characters peculiar to the gland elements from which they come, which are wholly anaplastic in other words, would be those which would fail to respond to orchidectomy or to the neutralization of the influence of testosterone with estrogenic compounds; and this has turned out to be the case. But Huggins has shown that even the most anaplastic cells still elaborate acid phosphatase, a normal function of the prostatic epithelium. Evidently they are not lost to all good, and it may be possible to find ways experimentally to play upon what might be called their better impulses.

There are other instances in which the formation and the success

of tumors is consequent on the stimulating influence of hormones. Certain testicular neoplasms of mice will not grow after transplantation unless the new hosts are injected with estrogen. A few years ago it was noted that uterine myomas develop in guinea pigs thus injected, and Lipschütz, working in Chile, has now demonstrated that testosterone will prevent the growths from appearing. Whether this has a practical bearing remains to be seen.

It is a curious fact that while hormones play a large role in tumor production and behavior little has been found as yet which the vitamins do. This is not for lack of tests with them.

The dependence of some tumors on hormonal influences for success justifies the inference that the change of a normal cell to a tumor cell does not necessarily mean that a growth will arise; and proof in the matter has been accumulating recently. Most of the tumors which appear on skin exposed to carcinogenic agents require favoring conditions if they are to grow, and the carcinogen itself provides these by setting up a chronic local inflammation productive of hyperplasia. After the carcinogenic applications are stopped many or all of the induced growths, including squamous cell carcinomas, may disappear rapidly as the local disturbance wears off. The course of those growths that progress and later prove highly malignant is often hesitant in the beginning. If the caloric intake of mice is cut down somewhat, so that the animals appear fit instead of fat, though slightly smaller than usual, the carcinogenic hydrocarbons induce relatively few tumors on their skin and these appear much later. This is not because the agents have failed to bring about neoplastic changes; for if the animals are full-fed later, tumors rapidly start forth although the carcinogen has not again been applied. The "spontaneous" pulmonary growths to which mice are liable can also be prevented from appearing by moderate restriction of the food intake. It would be worth while to know whether the incidence of cancer has fallen off in the starving populations of Europe. At the moment much work is under way to learn whether modifications of the diet which involve no caloric reduction will hinder tumor growth.

In proportion as a tumor continues to grow, cutting down the food is less effective in hindering it. This is in part because the best equipped cells tend to come to the fore as proliferation goes on, and in other part because secondary neoplastic changes, superimposed on the first and always for the worse, may render the tumor more aggressive. Often

cancers seen in the clinic are the end result of a series of untoward happenings and have been "babied along" by this influence, or that circumstance. It is no accident that most of the precancerous states observed in man provide conditions notably favorable to cell proliferation. And yet most of the cancers seen by the surgeon are not doing all of which they are potentially capable, as witness the stimulating effect upon them later of trauma, necrosis, ulceration, bacterial infection. Ultimately however, some of them become superior to their circumstances; many cancers grow with exceeding swiftness in their final stages, though the patient wastes. Much has still to be found out concerning the adjuvant influences which make clinical cancers worse. Without doubt some of these influences can be excluded or combatted.

These facts lead on to a conclusion of large practical import, namely, that the cells of not a few malignant growths can be held in check, kept from dividing, if steps are taken while they are in the early, hesitant stage; and to hold them in check is, in effect, to prevent the cancers. The systematic examination with the microscope of human prostates has shown that carcinomas are frequently present in them which never cause trouble. Not only should a tumor be got at early because then it is small, but because then it is different, a far less capable threat intrinsically. Even the smallest details in the previous history of cancer patients, no matter how far back, may prove vital for other human beings, as giving hints about where the chain of events can be broken which leads on to the disease. Too much pains cannot be spent in eliciting such histories. There should be specialists in every cancer hospital whose duty and ambition it is to learn precisely how each patient's tumor has come about. For just beyond such knowledge lies prevention.

Numerous discoveries might be mentioned which perhaps have a greater claim to attention than those here dealt with; the years will show. But at the moment most of these have only the status of random facts, facts with no setting, what might be called knick-knacks of knowledge because how they fit into it is not yet clear. What is the meaning, for example, of the discovery made in France by Lacassagne that Roentgen rays applied in very small amount to the leg muscles of rabbits, at spots where a pyogenic infection has healed a year or two previously, often lead to the appearance of sarcomas? There is more here besides a hint to practitioners of radiology. And what of the finding that general anesthesia with urethane, lasting only a few hours,

is followed by the rapid appearance of multiple lung tumors in mice of the breeds liable to occasional growths of the sort? And why should urethane, though provoking lung tumors in mice, actually hinder the course of human leukemia? Each of these well-attested observations means something, perhaps something large, but no one can say now what it is. Any new fact about cancer is worth while, and the growing heap of knick-knacks assuredly holds treasures. The authenticated advances themselves have been largely episodic in character. Yet there is a feature common to most of them which bodes well for the future; they are not the reward of random strivings but of intent and purposeful head-work. They give the physician good reason to look forward to the day when knowledge of cancer will come to be power.

LYMPHOMAS AND LEUKEMIAS*

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EVERY doctor in practice, no matter what kind of practice he is in, is surely going to see some aspect of that wide range of disease processes that are included in this title, lymphomas and leukemias, for the reason that they can affect any part or function of the body, and can mimic many other diseases. Obviously, therefore, lymphomatous and leukemic disease processes should occupy an important compartment in every doctor's knowledge of medicine. Yet, not only does there seem to be a considerable degree of unfamiliarity with these diseases, bred from a belief that they are too rare to merit much attention, but they seem to connote in many practitioners' minds a particularly bad prognosis in the field of cancer.

My purpose in this discussion is to give to the diseases included in the terms lymphomas and leukemias their proper share of recognition in a program devoted to cancer, about which there is now so much interest and hope, and to show that the prognosis may be far better than is generally assumed.

A few cogent reasons will serve to emphasize the importance of this group of tumors of the lymphatics and blood-forming organs.

1. To a large extent, they strike down persons whose lives are just opening before them—infants, adolescents, and young adults—and thus are of greater economic and social impact than are diseases which affect mainly the aged.

2. They are not so rare. Reports of wards in army and navy hospitals that contained 60 patients with Hodgkin's disease at one time make one realize that here is a real problem affecting largely our youths. Louis Weiner, chief of the statistical division of the Department of Health of the City of New York has kindly furnished figures for the deaths from Hodgkin's disease, lymphosarcoma and leukemia in New York City for the years 1940 to 1945 inclusive. These figures show that

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TABLE I—78157 DEATHS FROM MALIGNANT TUMORS IN NEW YORK CITY, YEARS 1940-1945

	<i>Deaths</i>	<i>%</i>
Hodgkin's disease	928	1.2
Lymphosarcoma	1346	1.7
Leukemia	2735	3.5
<i>Total</i>	5009	6.4

to all malignant tumors Hodgkin's disease deaths bore a ratio of 1.2 per cent, lymphosarcoma 1.7 per cent, and leukemia 3.5 per cent. Thus taken together they account for 6.4 per cent of all deaths from cancer or about one case in every 16 (Table I).

3. Their ability to affect any tissue or function of the body means that not only every general practitioner, but every specialist as well, must be prepared to consider these diseases in his decisions about diagnosis and treatment.

4. There is evidence for at least the theoretical possibility of cure of early localized Hodgkin's disease and lymphosarcoma.

5. There is evidence of decidedly worthwhile greater palliation and prolongation of life resulting from precision of treatment methods based on more knowledge of the pathologic anatomy and on close follow-up of patients.

6. These diseases lend themselves well to clinical investigation of cancer and trial of new therapeutic methods. For example, if we can discover the secret of the leukemia cell we may be a long way on the road toward an understanding of the malignant neoplastic process in general.

An example of the way in which trial of new therapeutic agents on lymphomatous disease may yield unexpected dividends was the discovery last winter that nitrogen mustards, known to have palliative effects in varying degrees on lymphomas, especially Hodgkin's disease, could also exert marked palliative effects on anaplastic bronchogenic carcinoma.

7. Last, but not least in the reasons for the importance of these diseases, is the thought that, while in the mind of the practitioner, one of these diseases, when encountered, may elicit only an attitude of sympathy for what he believes to be a hopeless outlook in a rare disease, yet, to the patient who has it, the disease is of prime importance and

its rarity of no consolation. There would be no question of the patient's choice, as between condemnation to one or two years of hopeless invalidism if nothing, or too little is done, and the chance, although not the guarantee, for 3, 5, or perhaps even 10 or 15 years of comparative comfort, if not cure, if his treatment is prompt, and followed up regularly.

These diseases, the lymphomas and leukemias, stand so rather apart in the field of malignant tumors, by virtue of their peculiarities, that it has often seemed to the writer high time that some sort of special institute or hospital be organized to study and treat them.

In dealing with so complex and poorly understood a group of diseases it becomes desirable to formulate a sort of philosophy about them—to keep in mind a general concept as an aid in approaching problems of diagnosis and treatment. At the same time it is not helpful to think of them under the single concept of lymphoblastoma or leukemia. We should want to know in any specific case whether we are dealing with Hodgkin's disease or lymphosarcoma, with mycosis fungoides or myeloblastic leukemia, with polycythemia vera or erythroleukemia.

Although we try to fit each case into a specific category, we have to recognize that borderlines are not sharply drawn. What is today in this patient a case of Hodgkin's disease may 5 years from now prove to have evidence of giant reticulum cell sarcoma. The case that today is one of giant follicle lymphoma, very radiosensitive, and seemingly curable by moderate x-ray therapy, is practically certain in 2 to 10 years from now to be a case of relatively radioresistant reticulum cell sarcoma. In the case that has a generalized lymph node enlargement, with a biopsy showing lymphosarcoma, and with a blood count showing lymphatic leukemia, shall we call the disease lymphosarcoma, or lymphatic leukemia, or shall we compromise and call it lympholeukosarcoma?

Not only do we have these indistinct boundaries between what would otherwise be distinct entities, and not only do we have these transitions, apparently from one condition into another, but we are confronted many times, also, with cases apparently lying on the borderline between inflammatory processes and true lymphomas and leukemias.

It is not at all uncommon to find that there is difficulty both in the clinic and in the pathology laboratory in making such distinctions as between tuberculosis and Hodgkin's disease, Boeck's sarcoid and Hodg-

kin's disease, Boeck's sarcoid and lymphosarcoma, brucellosis and Hodgkin's disease, atypical infectious mononucleosis and lymphosarcoma, dermatopathic lymphadenitis and Hodgkin's disease.

An unusual example of the confusing overlappings in this field is afforded by a patient now under treatment, who in the course of about six years has provided our pathology service with lymph nodes suggesting at one time tuberculosis, another time follicular lymphoma, then specimens from partial gastric resection and liver biopsy diagnosed sarcoidosis, and most recently another lymph node biopsy that showed Hodgkin's disease!

One part of the philosophy of these diseases, then, is to think of them in dynamic and functional terms rather than as static pathologic entities, recognizing that the lability of their tissues and cells of origin—marrow, spleen, nodes and reticuloendothelial system—endows them particularly from the beginning with a property of being in a state of flux, no doubt stimulated or inhibited by various hormonal or other factors, whose modes of action are as yet little known.

Only by reference to these unknown factors of growth stimulation and control can we lamely account at this time for such variations as those which permit one patient with generalized lymphosarcoma to do well for years with a minimal amount of x-ray therapy, while another with no appreciable difference in histology of tumor, or amount of disease, progresses rapidly to fatal outcome.

Another more practical part of the philosophy has to do with the premise that Hodgkin's disease and lymphosarcoma, and particularly Hodgkin's disease, give evidence of arising often in a single focus and that generalization takes place by spread from that initial focus, as in other malignant neoplasms. There is perhaps some basis for a belief that even leukemia may start at one focus, but if so it is never recognizable, until it is a generalized disease. While admitting that in some cases of Hodgkin's disease, and perhaps in the majority of cases of lymphosarcoma, there may be either a multicentric origin, or at any rate such a rapid generalization that it almost amounts to the same thing, yet there does seem to be evidence for the unicentric origin of most cases of Hodgkin's disease and some cases at least of lymphosarcoma.

In Hodgkin's disease, for example, any clinic that has treated a considerable number of cases over a period of 20 years or more can cite cases in which the disease has been treated adequately when fairly early

and regionally localized, and in which there has been long survival and little or no spread of the Hodgkin's process beyond those sites in which it was originally found and treated. A woman who had mediastinal and supraclavicular Hodgkin's disease, treated vigorously for about 3 years, then went for 15 years with no apparent need for treatment, only to have Hodgkin's disease then recur in the mediastinum and after 4½ years eventually kill her by intrathoracic spread, pleural effusion and cardiac failure, but at autopsy there was no sign of Hodgkin's disease below the diaphragm. Thus she had a total course of 22½ years following the first treatment, with persistently regional localization of the disease.

Of course such cases are exceptional, and no doubt may possess some inherent factor that, in addition to the intensive early treatment, tends to inhibit spread of the disease, but at the same time they do support the thesis that Hodgkin's disease or lymphosarcoma may arise in one focus, and that if the original localized disease is in such a location that it is amenable either to complete surgical removal followed by x-ray therapy, or to obliterative roentgen therapy, there should be a possibility of cure.

In contrast with these early localized types we have the cases that still comprise the bulk of what we have to treat, those in which the disease is widespread. This includes, of course, all the leukemias and most of the cases of mycosis fungoides, lymphosarcoma and Hodgkin's disease. Leukemia when diagnosable is always a generalized disease, while the others may have a greater or lesser degree of generalization. The philosophy in these generalized forms is to accept at once the incurability of the process by any means known today, and so to design the treatment as to gain the best and longest palliation. Yet in Hodgkin's disease and lymphosarcoma, the majority of cases when first seen present a setting somewhere intermediate between strict, unifocal localization and universal generalization. Those with a nearer approach to regional localization may do well with fairly-intensive local therapy, while those with very widespread disease may have to be treated quite circum-spectly.

In this whole field results today in palliation can be much better than they were two decades ago, mainly because of greater knowledge of and consequently search for obscure lesions, the control of which is at least as important, if not more so, to the patient's well-being, as the

control of the more obvious lesions. We no longer think of Hodgkin's disease and lymphosarcoma as diseases of the lymph nodes alone, or of leukemia as a disease of marrow, spleen, nodes and blood alone, but rather as processes that may produce lesions of any organ or tissue.

In order to stress the liability of the lymphomas and leukemias to affect any tissue or organ, let us review some of the data we have.

Skin: Mycosis fungoides—or granuloma fungoides is often spoken of as not an entity, but as merely a cutaneous manifestation of so-called lymphoblastoma. It seems preferable, however, to preserve this name as indicative of a more or less distinct entity. Mycosis fungoides follows a rather distinctive natural course, arising often on the basis of a long standing chronic eczematoid rash, beginning as low infiltrated plaques and progressing to fungating thick cutaneous tumors. The natural history may be very long, upwards of 20 years. Some cases referred to by the French as mycose fungoïde d'emblée arise as tumors of the skin unheralded by the more common preexistent chronic eczema.

In our experience, the earlier cases are diagnosable histologically, while the older cases show a microscopic structure of reticulum cell sarcoma. We have never seen this condition as part of Hodgkin's disease, or leukemia. If it must be regarded as merely part of so-called lymphoblastomas, it should be classed with lymphosarcoma, but its long course is quite at contrast with the average lymphosarcoma, and therefore, from the point of view alone of analysis of 5 year survival curves, it should be kept separate.

One of the clinical varieties of lymphosarcoma that is often mis-handled is the type that begins with perhaps only one small insignificant looking, slightly pinkish or purplish plaque in the skin, especially of the scalp. Such a plaque may exist for a year or two before anything else develops, and if not biopsied, may readily be regarded as of no consequence. A few months ago we saw one that had been vigorously squeezed by a physician who thought it was a sebaceous cyst. Yet such an unimpressive lesion may be the first signal of a process that sooner or later will generalize, involving external and internal lymph nodes, spleen, liver, bone, lungs, and other tissues, and eventually kill the patient. However, some of these cases are much less malignant, and can be controlled for long periods by local irradiation.

Hodgkin's granuloma in the skin is relatively uncommon, but may assume bizarre forms, varying from single or multiple plaques and

nodules, non-ulcerated or ulcerated, to broad, diffuse erythematous lesions. In a few cases it may exactly mimic multiple tuberculous abscesses with large irregular necrotic ulcers having serpiginous edges. In some cases there will appear rather rapidly a group of tiny shotty nodules in or just beneath the skin, usually about the upper chest wall. Cutaneous lesions of Hodgkin's disease usually yield well to irradiation.

Herpes zoster is an old acquaintance in this entire field. It has been recognized for many years that herpes zoster has an uncommonly high incidence in cases of lymphoma and leukemia. Occasionally along with classical herpes zoster, there is also a generalized herpes, with varicelliform lesions. Although the literature contains references to examples of cross infection with chicken-pox, we have never found a clear cut instance of such mode of infection.

Leukemic infiltration of the skin is fairly common, especially in lymphatic leukemia. Purpura may exist with or without a reduced platelet count.

A remarkable series of rare cases are what we have called our red Indians. These patients have red, thickened, scaling skin, enlarged lymph nodes and a white blood count suggesting chronic lymphatic leukemia. Apparently some have true leukemia, and some do not, but whether eventually all will become leukemic, we do not know. One such patient, a man, had on two occasions, a remarkable clearing of his skin lesions, and restoration to normal blood count following the administration of estrogens, but later died, apparently having true leukemia. Another such case was reported by Fraser as having a mistaken diagnosis of leukemia, because he had apparently a complete spontaneous remission.

The gastro-intestinal tract may be involved anywhere from mouth to anus by various primary or secondary lesions of the lymphomas, and by various infiltrations or secondary manifestations of the leukemias. Marked swelling and necrosis of the gums, if the patient has a leukemia, has come to arouse always a suspicion that the leukemia may be monocytic.

Hodgkin's disease and lymphosarcoma apparently primary in stomach or bowel have been successfully removed surgically with resultant long survival.

In a series of 36 autopsies in Hodgkin's disease, five showed lesions of the gastric wall, and one had a healed-over duodenal ulcer, the base

of which showed Hodgkin's disease. In a series of 406 proved cases of Hodgkin's disease, about 13 per cent complained of gastro-intestinal symptoms. In many instances these symptoms are caused by intra-abdominal disease that remains extrinsic to the gastro-intestinal tract. The lesions, either intrinsic or extrinsic, may be favorably affected in varying degrees by external irradiation with x-rays, and in some cases may be made to disappear entirely.

The genito-urinary tract is not immune to attack by lymphomatous or leukemic disease. At autopsy leukemia is often found extensively infiltrating the kidneys. Nemenov proposed years ago that in treating leukemia by irradiation, one should first give moderate doses to the kidneys in order to improve their function by decreasing their leukemic infiltration.

Retroperitoneal lymphomatous nodes may so infiltrate as to encase kidneys, adrenals, and ureters in one dense thick mass. Recently we have observed Hodgkin's disease in and about the female urethra. Last year 3 large, polypoid tumors arising from the vaginal wall, and very radiosensitive, proved however, to be the first evidence of a rapidly fatal myeloblastic leukemia.

Following such a complete remission of acute leukemia in a young boy that for a short time we trusted we had been dealing with a leukemoid reaction to infection, the first evidence of return of activity of leukemia was a bilateral hard testicular enlargement to four times normal size.

Priapism is mentioned in all the books as a complication of leukemia, but actually is of rare occurrence.

Whether a young woman having one of these diseases should marry is a question that arises several times a year. This is a delicate matter, since as a rule the patient herself is purposely kept ignorant of the prognosis and if possible even of the name of the disease, although some responsible member of the family is kept informed. With the patient's permission, the fiancé is told all about the disease, and instructed to see to it that the patient does not become pregnant.

If, when the young woman patient is first seen, pregnancy has already occurred, we do not in general advise a therapeutic abortion—certainly not if the pregnancy has gone beyond four months. If pregnancy is earlier than three months, decision about therapeutic abortion should be made on the basis of individual circumstances. In Hodgkin's

TABLE II—PULMONARY PARENCHYMAL LESIONS OF LYMPHOMAS AND LEUKEMIAS

	<i>Roentgen findings per cent</i>	<i>Autopsy findings per cent</i>
Hodgkin's disease	38.5	47.0
Lymphosarcoma	29.6	24.5
Lymphatic leukemia	26.5	19.0
Myelogenous leukemia	7.6	13.0

ALL INTRATHORACIC LESIONS OF LYMPHOMAS AND LEUKEMIAS

	<i>Roentgen findings per cent</i>	<i>Autopsy findings per cent</i>
Hodgkin's disease	75	88
Lymphosarcoma	54	73
Lymphatic leukemia	72	84
Myelogenous leukemia	18	48

disease there seems some reason to believe that the termination of pregnancy, spontaneously or artificially, at full term or prematurely, gives a stimulus to the disease. However, this impression may have been caused by the added growth of the disease that perforce has been allowed to take place in some cases during pregnancy because the existence of the pregnancy led to withholding treatment of lesions that otherwise would have been treated and kept more or less under control.

One is naturally reluctant to use irradiation about the abdomen or pelvis of a pregnant woman, for fear of injury to the fetus. For the treatment of leukemia in a pregnant woman Forkner has suggested that arsenic be used, rather than irradiation.

Respiratory tract: Any part of the respiratory tract may be affected by any of the lymphomas or leukemias. Mediastinal and hilar lymph node enlargement is so common, except in myelogenous leukemia, that it need not be discussed. It may be noted that in a survey of chest films in 52 cases of myelogenous leukemia, no mediastinal tumors were found, and discrete hilar nodes were noted in less than 10 per cent. However, in a series of 23 autopsies of cases of myelogenous leukemia, myeloidi-

zation of enlarged mediastinal or hilar nodes was found in 47 per cent.

Considering the more obscure and less often thought of lesions of lung parenchyma, a considerable discrepancy may be noted between roentgenographic findings and autopsy findings. This discrepancy naturally is explainable in part by the terminal advance of pulmonary lesions which were not visible when the patient's last chest films were made. Nevertheless, the discrepancy is large enough to suggest that lesions were often missed because chest films were not taken at appropriate times. (See Table II.)

It is perhaps not well enough known that cavitation can occur in Hodgkin's disease of the lung. Not only may abscesses form distal to bronchial obstruction by Hodgkin's disease, or secondary to such rare developments as tracheo-esophageal fistulae, but central break-down can occur in either large or small Hodgkin's nodules in the lungs and produce cavitation with or without the influence of infection or irradiation.

The intrathoracic lesions as found at autopsy have been classified, following Versé, as follows: Mediastinal node lesions, hilar node lesions, mediastino-bronchial node lesions with direct invasion of the lung, mediastino-bronchial node lesions with peribronchial and intrabronchial spread, more or less lobar (diffuse) infiltration of the lung with varying degrees of involvement of the broncho-mediastinal nodes, confluent lobular (isolated circumscribed) focal formations with involvement in various degrees of the broncho-mediastinal nodes, miliary (lympho-hematogenous) foci with involvement in varying degree of the broncho-mediastinal nodes, parietal pleural nodules, and pleural effusion.

It is of interest to note that occasionally in Hodgkin's disease, the intrabronchial mode of spread may include an organization of endobronchial exudate into specific Hodgkin's granulomatous tissue.

Lesions in the chest wall may arise either as rib lesions growing both internally and externally, or they may arise as pleural nodules growing out through the chest wall, to involve ribs, muscle, and subcutaneous tissue.

The intrathoracic lesions, particularly those of the tracheobronchial nodes and central lung parenchyma may be silent for months, even though of considerable bulk, and readily detected roentgenographically, yet they, like other visceral lesions, may be prognostically much more serious than the external nodes to which a disproportionate amount of attention may be paid.

The lesions of the lung and pleura may not respond as well to x-ray therapy as do superficial nodes or even mediastinal nodes. It seems likely that the character of the tissue bed in the lung or pleura accounts for this tendency to show a less favorable response. However, in many instances the regression after irradiation is gratifyingly rapid and seemingly complete.

When a pleural effusion occurs on one side it appears preferable to try first the effect of irradiation, rather than to resort to thoracentesis immediately. In many cases, the effusion will absorb rapidly following irradiation, whereas following thoracentesis, usually the fluid re-accumulates rapidly, and in these cases there seems to be particularly a tendency to multiloculation of the fluid following thoracentesis.

The skeletal system: While marrow infiltration becomes universal in leukemia, and is common in Hodgkin's disease and lymphosarcoma, especially in the later phases, it is when cortical bone becomes affected that the patient is particularly liable to develop severe pain or disability, demanding relief. Figures of the incidence of gross bone lesions affecting cortex have varied widely, and are probably all too low. In Hodgkin's disease reports in the literature of bone lesions found by roentgen examination run around 16 to 20 per cent. It is my own belief that 50 per cent would be nearer the truth, if such lesions were regularly searched for.

The most common type of cortical bone lesion found in Hodgkin's disease is a mixture of osteolytic and osteoplastic change, occurring in half of those cases in which bone lesions are found. The second most common type, representing about 2/7 of the cases with bone lesions, is a purely osteolytic change; and the least common type, comprising about 1/7, is a purely osteoplastic change.

In lymphosarcoma the mixed type, showing both destruction and production of bone, makes up only 1/10 of the cases with gross bone lesions, while the purely osteolytic type accounts for 85 per cent, and the osteoplastic type only 5 per cent.

Thus, contrasting lymphosarcoma with Hodgkin's disease, if a gross bone lesion develops it is three times as likely to be purely destructive in the case of lymphosarcoma as in the case of Hodgkin's disease, and only about one third as likely to be of the purely productive type.

Extensive bone changes in the skull, or in the vertebral column, even with fracture and collapse of vertebrae, may be accompanied by

no other neurological affection than pain.

Prompt relief of pain and in some cases complete or nearly complete restoration of normal roentgenographic appearance of the diseased bone may result from early treatment of these lesions by irradiation, before any deformity has occurred.

The early recognition and treatment by irradiation of the bone lesions complicating lymphomas and leukemias constitute an important part of the improved palliative management of these diseases.

The bone lesions, especially those with extensive osteoplastic changes, may produce an elevation of serum alkaline phosphatase levels. However, the determination of alkaline phosphatase is no longer regarded as of much significance in this field, because so often the patient with bone lesions has impaired liver function, which likewise is reflected in an elevated phosphatase level.

Nervous system lesions of the lymphomas and leukemias constitute a large chapter in themselves. Any of the special sense organs and any part of the central or peripheral nerve system may be directly or indirectly affected by any of these diseases.

Some of the more common or more serious manifestations of neurological lesions deserve brief mention.

Paraplegia may develop fairly rapidly unaccompanied by any detectable gross lesion of the spinal column. If x-ray therapy is given accurately and promptly over the appropriate level in adequate doses, paralysis may disappear more or less completely. For example, a woman with Hodgkin's disease who had complete paraplegia in the summer of 1939 was able to walk in a few weeks and after a few months all signs disappeared except moderate exaggeration of knee jerks and for years she has walked and climbed stairs normally.

Herpes zoster may be extensive and painful, and may produce large necrotizing lesions that leave many deep scars. Some relief may be afforded by prompt x-ray treatment of the appropriate level of the spinal cord.

Sixth nerve paralysis seems fairly common, as does a partial fifth nerve affection producing anesthesia about the chin.

Horner's syndrome is often seen accompanying enlarged nodes at the base of the neck anteriorly.

Lenk has stated that it is so unusual for Hodgkin's nodes to cause phrenic nerve paralysis that the discovery of such paralysis speaks against

a diagnosis of Hodgkin's disease. However, either phrenic or recurrent laryngeal paralysis may occur in any of the lymphomas or leukemias, being seen particularly with Hodgkin's disease and lymphosarcoma.

Pruritus, so common in Hodgkin's disease (about 30 per cent), and not infrequently seen in other lymphomas and in lymphatic leukemia, while usually more or less general, may in some cases be regionally distributed in such a way as to suggest a neurological basis. Itching should always be regarded as a sign of the presence of active disease.

In one case of Hodgkin's disease a completely intractable and severe peripheral neuritis made the patient's last year of life miserable.

Retinal hemorrhage may be the first clue to an acute trend in a leukemic patient.

The apparently benign orbital lymphoma may be followed in a few years by generalized lymphosarcoma.

Jaundice develops from various causes in many patients with lymphomatous or leukemic disease. It is often well nigh impossible to know how much to blame, respectively, hepatitis, which may be of the homologous serum variety in those who have received transfusions, or portal obstruction, or hemolysis, as the factor responsible for the jaundice, since the usual tests may fail to give a clear answer, and there is often reason to believe that all possible factors or some combination of them is responsible.

Ascites and marked edema of the lower extremities are very likely to occur in the patient who not only has ample reason for these phenomena on the basis of obstruction by enlarged nodes, but also has marked hypoproteinemia.

Anemias of various kinds are encountered in these diseases. Although some may be relieved by iron, by improvement in diet, by liver or transfusions, yet many, apparently caused mainly by irreversible marrow impoverishment, persist despite all measures. Although we have used transfusions much more in recent years, it is not clear that a great deal more has been accomplished thereby, and certainly it is true that one runs into a high incidence of both immediate transfusion reactions and hemolytic states, that tend to cast some doubt on the efficacy of transfusions if used on a large scale for these diseases. Not at all uncommon is it to find that a patient with leukemia has a lower red cell count following transfusion.

The hemorrhagic diathesis is particularly troublesome in leukemia,

especially in the acute cases, and in the acute exacerbations of the chronic cases, but may occur in any of the other diseases under consideration. It is usually, but by no means always, accompanied by a reduced platelet count, and in many cases the platelet count may be below 50,000, and yet no evidence of bleeding tendency will be found. It seems most likely that the bleeding is more often dependent on damage to integrity of vessel walls than any other factor. There is no single satisfactory method of overcoming the bleeding tendency, and in most cases the use of vitamin K, or C, thromboplastin, fibrin foam, calcium, or Koagamin is ineffective. The value of rutin remains to be tested.

Hypoproteinemia is often a serious problem in the more advanced cases, and in many of these is most refractory to treatment. It often is partly responsible for edema in a patient whose abdomen is so full of lymphomatous disease that pressure is also partly responsible for the edema. Such a patient may be unable to eat, and unable to respond to transfusions of blood or plasma or infusions of casein hydrolysates.

The basal metabolic rate may be considerably elevated, not only in leukemia but in Hodgkin's disease and lymphosarcoma, especially in the more active cases. Some years ago, attempts were made to treat leukemia by thyroidectomy, but one hears no more about that today. Because of the effect of thiouracil in lowering the basal metabolic rate in hyperthyroidism and in occasionally causing granulocytopenia, it seemed reasonable to try its effect on leukemia, but no consistent beneficial effect was found.

About 20 years ago a rather dogmatic statement appeared in the literature to the effect that the level of the basal metabolic rate was the best indication for the treatment of leukemia, and that if the basal metabolic rate were high, the case could be safely treated, even though the white cell count were low. This statement seemed a rather dangerous one then, and although it has recently been reiterated, it still seems preferable to advise a broader perspective in treating leukemia than to depend on any such single sign. One can think of various situations, such as cases in a near terminal stage, cases of myeloid leukosarcoma, cases of myeloid leukemia with extensive lymph node myeloidization, always a bad prognostic sign, or those with pronounced bleeding tendency in which, although the basal metabolic rate would be markedly elevated; other factors would indicate great caution in radiation therapy or would

even indicate withholding it entirely.

Fever has been taken for granted as a common feature of lymphomatous or leukemic disease on the assumption that the disease itself directly causes the fever. The true Pel-Ebstein cycle of regularly recurring febrile and afebrile periods is a striking phenomenon when seen in Hodgkin's disease, but actually is not very common. Practically every patient with Hodgkin's disease, lymphosarcoma or leukemia has bouts of fever at some time during the course, but as a general rule, the fever follows no distinct pattern. Considering the frequency with which intercurrent or terminal infections occur, the occasional marked response to sulfonamide or penicillin therapy, and the known impairment of the reticuloendothelial system in these diseases, it is a matter for speculation whether the fever is actually directly due to the lymphomatous or leukemic process, or whether it may not indicate lowered resistance to invasion by bacteria or their toxins.

Diagnosis is notoriously difficult in lymphomas and leukemias. While there are many clean cut cases, about which there is no diagnostic uncertainty, yet there are many others about which even the most skilled tumor pathologists will disagree. The possibility that Hodgkin's disease and lymphosarcoma may clinically simulate or be simulated by other diseases, makes it particularly necessary to obtain proof of diagnosis histologically, if at all possible.

Lymphosarcoma has been simulated by neuroblastoma, cancer of the pancreas, liposarcoma, and various other widely dissimilar tumor processes. It is often difficult to differentiate clinically between bronchogenic carcinoma and Hodgkin's disease. Tuberculosis or Boeck's sarcoid may exactly simulate Hodgkin's disease, and vice versa.

Even leukemia may be masked at first. It is often difficult to say where refractory anemia leaves off and leukemia begins. Recall that malignant tumors metastatic to bone may cause the appearance of some immature blood cells in the peripheral blood. Enlarged lymph nodes in a patient with a leukemic blood picture may show carcinoma rather than leukemia. Too, the presence of both leukemia and cancer, or of a lymphoma and cancer, in the same patient is not so rare. It is a good general rule, that whenever a patient with chronic leukemia or lymphoma does not respond to treatment as well as was expected, one should look particularly for some obscure cancer.

The diagnosis of leukemia may in most cases be fairly well estab-

lished by examination of the peripheral blood alone, but it is usually advisable to examine as well thin smears of 0.1 or 0.2 cc. of sternal marrow obtained by puncture. Sternal puncture may be of decisive value in many doubtful or clinically borderline cases. Yet in the interpretation of the marrow obtained by the puncture method, one must always keep in mind that to a greater or less extent there is an admixture of circulating blood. Thus in the cases with a node biopsy showing lymphosarcoma and a blood count suggestive of lymphatic leukemia, say 25,000 white cells with 75 per cent small lymphocytes, the finding of about 50 per cent lymphocytes in the marrow smears has to be somewhat discounted because, obviously, so many of the lymphocytes are there because of the admixture of circulating blood. Occasionally it is preferable to obtain a surgical biopsy of the marrow.

If any accessible enlarged nodes are found it is usually advisable, in order further to round out the diagnosis, to do a biopsy of the node.

The following example illustrates the value of having, wherever possible, a check on the diagnosis in these three ways, lymph node, peripheral blood, and sternal marrow. A patient with a general lymph node enlargement came in with a node biopsy that was interpreted at first as lymphosarcoma. Then it was noted that the blood smears showed some immature myeloid cells, whereupon a marrow puncture was done, and showed myeloblastic leukemia. With this information, reexamination of the node disclosed that the cells that resembled lymphosarcoma cells were of myeloid origin. The practical importance of this differentiation lay in the ability to know thus early that we were dealing with an aggressive case of myeloblastic leukemia with extremely bad prognosis and practically a contraindication for vigorous x-ray treatment, rather than with a case of lymphosarcoma, in which x-ray treatment might have offered a good prognosis for temporary control of the disease.

In lymphosarcoma and Hodgkin's disease the diagnosis must be based, if possible, on biopsy of a representative node. Too often, for cosmetic reasons, a small outlying node is selected that fails to yield a satisfactory specimen. With experience one learns to be able to select whichever small peripheral and easily accessible nodes are likely to be significant, judging them by their change to globular or nodular shape and firm to hard consistency, but without such experience, it is better to select, if possible, a node which has been enlarged longer, and is part of a group of nodes, so that it seems likely to be more certain of

being representative of the disease process one is trying to identify.

In general, a formal surgical biopsy is to be preferred. Sometimes there is only one large fused mass of nodes with no single node available for dissection. In such cases a wedge may be removed. It is better practice in such a case to retract the skin so that the incision in the skin will not overlie the incision in the capsule of the tumor. There will then be less danger of fungation of the tumor through the wound.

Many cases of lymphomatous disease are seen in which there is no peripheral node available for surgical biopsy. The patient may have only one small node behind the inner end of the left clavicle at the junction of the thoracic duct with the subclavian vein—the signal node. He may have only a mass projecting from one side of the mediastinum. He may have only an enlarged firm spleen. In such cases an aspiration biopsy may yield a specimen that is quite satisfactory to a pathologist who has been willing to make himself competent in the interpretation of such material.

In a review of biopsies in 242 cases of proved Hodgkin's disease, aspiration biopsy was selected as the first method to try in twenty-five cases, and was diagnostically successful in fourteen cases, or 56 per cent. In the eleven unsuccessful cases the aspiration biopsy failed to yield sufficient or satisfactory material, and it was necessary to resort to a surgical excision. Even in most of the failures enough information was gained to suggest a lymphomatous process, and in some cases such reports as lymphoid tissue, or a question as between Hodgkin's disease and tuberculosis gave a lead pointing away from a previously considered diagnosis of carcinoma. As showing the value of biopsy by such a simple method in the differential diagnosis of clinically difficult cases, it is of interest to note the provisional diagnoses that had been made in a small series of nine cases in which aspiration biopsy proved the presence of Hodgkin's disease; namely, Hodgkin's disease in only one case, unspecified lymphoma in three, lymphosarcoma in one, tuberculous lymphadenitis in one, metastatic carcinoma in two, and carcinoma of thyroid in one. A successful aspiration biopsy diagnosis in fourteen of twenty-five attempts is not bad for this group of diseases, when one recalls that 10 years ago, when aspiration biopsy was already firmly established as an indispensable diagnostic method for many malignant tumors, a pathologist particularly experienced in this field would not attempt to diagnose Hodgkin's disease or lymphosarcoma on aspirated material.

The dangers of aspiration biopsy of the lung and spleen have been grossly exaggerated, although certainly they are not procedures to be undertaken lightly by the inexperienced. In the reported fourteen successful aspiration biopsies of Hodgkin's disease, three were obtained by puncture of the lung, and one was from the spleen. These were all cases in which, at the time the procedure was chosen, there was no other way of obtaining histological proof.

Treatment. Articles in the lay press about some of the newer forms of therapy suggest to the layman that the cure of lymphomatous and leukemic diseases is just around the corner, and in fact, many laymen have gained the erroneous notion that it should be possible now to effect a cure by these methods, and that all that is necessary is to find the specialist who has access to these new agents.

Particularly in the limelight at present are the radioactive isotopes, and the nitrogen mustards. It does seem certain that internal whole body irradiation, afforded by radioactive isotopes, and chemotherapy, probably with more effective compounds than the currently available nitrogen mustards, are methods of treatment that are here to stay. Both the radioactive isotopes and the nitrogen mustards have been shown to be useful tools, but neither method has as yet equalled the all around efficacy of roentgen therapy, when one considers all the different ways in which roentgen therapy can be used. Each has a certain field of usefulness now, and each can be regarded as a pioneer method, with the possibility that considerably greater effectiveness will be brought about by improvements. Clinical trial of nitrogen mustards was suggested because of the observations made by the Chemical Warfare Service that these agents produced a marked leukopenia, caused apparently by a selective destructive action on lymphatic tissue and bone marrow, and that this action on cells resembled that of roentgen rays. Clinical experience has shown that HN_2 (di-beta-chloroethyl amine) and HN_3 (tri-beta-chloroethyl amine) are useful chiefly in those cases of Hodgkin's disease in which generalization has begun, and constitutional symptoms are present. They are too toxic and too ineffective for use in the ordinary relatively early and regional case, in which x-ray therapy can bring about as a rule marked remission with relatively little toxic side-effect. To a less extent are the nitrogen mustards useful in very advanced cases of Hodgkin's disease that have become refractory to x-ray treatment, or in lymphosarcoma, lympholeukosarcoma, and

chronic lymphatic leukemia. They are of little or no use in myeloid leukemia, in any of the acute leukemias, or in the more aggressive forms of lymphosarcoma.

The radioactive isotopes that have been used for lymphomas and leukemias are chiefly radiophosphorus, and radiosodium, and recently radiomanganese. Our experience with radioactive isotopes in connection with this group of diseases has been entirely with radiophosphorus. Its chief field of usefulness is, in the order named, in polycythemia vera, chronic myelogenous leukemia, and chronic lymphatic leukemia. It has the advantage of causing no radiation sickness. Its great disadvantage is that it is not sufficiently selective, and its destructive effect on marrow is its limiting factor when large and repeated doses are employed. It does not in general treat lymphosarcoma satisfactorily, and almost uniformly its results in Hodgkin's disease have been disappointing. For all the acute leukemias radiophosphorus is hazardous, as is any other form of total body irradiation.

Neither the nitrogen mustards nor radiophosphorus can supplant roentgen therapy, and they are best regarded, not as competitive agents, but as complementary tools. The treatment of leukemia can seldom be exclusively carried out throughout the course by means of radiophosphorus. In most cases situations arise demanding x-ray therapy either as a supplement, or alone. It is most certain that nitrogen mustards could not alone control Hodgkin's disease. Their best use appears to be as a supplement to x-ray therapy. The usual early case with localized disease can be much better treated by local x-rays, and the same is in general true of the cases in an early stage of generalization, in which the disease is still relatively regional. When constitutional symptoms, such as fever and night sweats appear, then, provided the white cell count is reasonably good, nitrogen mustard may be an effective palliative agent, producing remissions lasting from two or three weeks to sometimes seven or eight months.

Another chemotherapeutic agent, urethane, was announced in *Lancet* last May, as effective in the palliation of leukemia. It was said to be effective in lowering the white cell count, to have more marked effect on the more immature white cells, and to reduce the size of the spleen. It was promptly tried in this country following publication by the English workers, but its effects have been disappointing. We have been unable to confirm any more marked effect on the less mature cells.

External irradiation, considering all its possible various forms, remains the most generally useful method of treatment of all the lymphomas and leukemias. This can still be said, while taking into account the many cases in which results are not satisfactory. The acute leukemias, for example, seldom derive any great benefit from radiation. Its use in acute leukemias may be totally contraindicated, or restricted to minor palliative measures, such as relief of pain caused by leukemic changes in bone, or relief of a complicating local infection of the skin, where the combination of infection and leukemic infiltration causes resistance to usual methods of treating infection, and where only treatment by a small dose of x-rays may cause the inflammation to subside.

Whereas lymphosarcoma used to be held up as the classical example of radiosensitivity, experience has shown that some cases may be rather radioresistant, and, moreover, there are certain very acute cases of lymphosarcoma that are so rapidly growing, and so complicated by fever, signs of infection and bleeding tendencies that they respond about as poorly as cases of acute leukemia.

On the other hand, there are certain very chronic, low-grade lymphomas and leukemias in which the question arises as to whether they should be treated at all, particularly since statistically it is difficult to produce evidence indicating any great prolongation of survival time as a result of irradiation. Especially in those chronic forms of leukemia in which the patient looks and feels well, or nearly well, does it seem doubtful that treatment should be advised.

Nevertheless, the great bulk of cases of Hodgkin's disease, lymphosarcoma and chronic leukemia have symptoms that are incapacitating, and need relief, and by and large irradiation in some form is the one agent that can best bring about that relief. Despite the failure of statistics to show any marked increase in survival time following irradiation, any one who has treated such diseases for many years could cite numerous specific cases in which there could be no doubt that irradiation had prolonged life for many years.

The range of ways in which roentgen therapy can be applied is indeed wide. Beginning with low voltage apparatus at 50,000 volts for treatment of superficial lesions, we can ascend the scale of voltage and penetration, through ordinary high voltage apparatus (180,000 to 250,000 volts), to the million volt machines useful for some bulky deep lesions, because it is a peculiar property of the supervoltage rays that

while delivering greater depth doses, they cause much less constitutional disturbance and much less skin reaction. Treatment with x-rays can be accurately applied to a circular field as little as 1 cm. in diameter, to an irregular area, or to very large fields. The whole torso or the whole body can be sprayed intermittently, or the whole body can be continuously treated for days or even weeks at very low intensity in the Heublein unit, where the patient receives irradiation in his bed day and night.

The Heublein method of external whole body low intensity prolonged irradiation by x-rays seems to add to the survival period and to the periods of remission in Hodgkin's disease, lymphosarcoma, and chronic lymphatic leukemia. Since 1940 interest in the internal, somewhat selective method of whole body irradiation afforded by radiophosphorus has tended to shunt cases away from the Heublein method, for which, however, there is still a place.

The results in Hodgkin's disease, lymphosarcoma, lymphatic leukemia and myelogenous leukemia have recently been surveyed for the 11 year period, 1930 through 1940, in terms of the 5 year survival curves. These figures reflect almost exclusively the results of therapy by means of external irradiation and general supportive measures, since our work with radiophosphorus did not begin until February 1940, and at that time no chemotherapeutic method was in vogue, except for the occasional use of arsenic for leukemia in moderate doses.

For the most part the net 5 year survival figures show an improvement over our previously reported results.

Hodgkin's disease shows 20.5 per cent 5 year survivals of 283 patients, as compared with 17.7 per cent for 265 cases from 1918 through 1935.

Lymphosarcoma shows 26.3 per cent of 308 patients surviving 5 years, as compared with 15.9 per cent of 132 cases for the years 1918 through 1933.

Lymphatic leukemia shows 15.7 per cent 5 year survivals of 125 patients as compared with 9 per cent reported for 77 cases from 1917 to July 1, 1929.

Myelogenous leukemia* shows 5.3 per cent 5 year survivals of 57 patients, as compared with 5.9 per cent reported for 68 cases from 1917

* The figures for leukemia, however, are not strictly comparable, since the later figures excluded very acute cases, and the earlier figures excluded only those lost to follow-up within 6 weeks.

through July 1, 1929.

Thus, there has been a decided improvement in the 5 year survival figures for Hodgkin's disease, lymphosarcoma, and lymphatic leukemia, while the figure remains unimproved for myelogenous leukemia. Just why there has been a failure to secure improved results in myelogenous leukemia is a matter for speculation. Possibly a greater proportion of the accepted cases has been of a somewhat more acute variety. Then, too, in myelogenous leukemia, as far as radiation therapy is concerned, it is usually a matter of irradiation of spleen, sometimes of long bones, or of the entire body. Whenever in a case of myeloid leukemia skin nodules, or enlarged nodes, or a leukemic tumor appears, the case is pretty certain to have from then on a more acute trend, and the tendency is to be much more conservative with radiation. On the other hand, chronic lymphatic leukemia, lymphosarcoma, and Hodgkin's disease are more nearly alike in that they lend themselves better to the treatment of lesions anywhere in the body, and the discovery of a skin infiltrate, a destructive bone lesion, or a tumor in some atypical location is simply an indication for more treatment, rather than necessarily an index of acute trend and probable uselessness of further irradiation. Perhaps we should be more aggressive in attempting treatment of the more aggressive forms of myeloid leukemia.

In conclusion, it may be emphasized that leukemias and lymphomas are important because of their not inconsiderable mortality and morbidity, especially among the younger elements of the population, because their range of morbidity brings them within the scope of every kind of practitioner, and because they are increasingly valuable to the investigation of the cancer problem.

They may now be more hopefully regarded, because as methods of diagnosis and treatment have approached greater precision we begin to detect promises of curability in certain types of Hodgkin's disease and lymphosarcoma, and appear to have demonstrated greater palliative and life prolonging effectiveness of therapeutic methods for most of the members of this heterogeneous family of diseases.

TUMORS OF THE STOMACH * †

ARTHUR PURDY STOUT

THE stomach is a neuro-muscular pouch provided with a powerful sphincter muscle at the pylorus where it joins the duodenum. In the proximal two-thirds, called the fundus, it is lined by a complex mucous membrane which is provided with a large number of highly specialized cells which secrete the acid and ferments of the gastric juice. These are surmounted by a thin layer of short pits or tubes from the cells of which a protective layer of mucus is produced. In the distal third of the stomach called the antrum and pylorus the gastric pits are much lengthened and the specialized cells correspondingly reduced so that here, where the food is made ready for propulsion through the pyloric sphincter, much mucus and little gastric juice is secreted. The mucosa and its vascular submucosa are loosely attached to the muscular walls and are thrown up into folds or rugae provided with a slender muscle of their own. The stomach is furnished with many blood vessels and lymphatics and a rich and complex nervous mechanism connected with the vagus and splanchnic nerves so that its activities are profoundly influenced by the activities of the organism as a whole.

The tumors which develop in the stomach are derived from the cells of the tissues which compose it. The vast majority of them are malignant and develop from the mucous cells. Attention will be focussed upon these and the rest must be dismissed with a word or two. The commonest benign tumors are the adenomatous polyps composed of mucous glands. These sometimes give symptoms but the most important fact about them is that they may become malignant. But polyps are rare in comparison with carcinomas. Tumors, most of which are benign, spring from the smooth muscle forming nodules which project both within and outside of the stomach. It is well to remember that when such tumors ulcerate they sometimes give rise to massive hemorrhages. The submucosal lymphoid tissue also gives rise to malignant tumors called

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† Read at the 19th Graduate Fortnight of The New York Academy of Medicine, October 1946.

lymphosarcomas. These grow in very much the same fashion as do carcinomas, produce comparable symptoms and are generally treated in the same way except that, since they are somewhat radiosensitive, radiotherapy is ordinarily used after their removal. There are other uncommon benign tumors of fat, connective tissue, blood and lymphatic vessels, nerve sheaths and from congenitally misplaced epithelial structures in the stomach wall.

Beginning sometimes as early as the third decade of life, processes of inflammation and atrophy commence to appear in the distal third of the stomach and may extend to the fundus. These can be divided into (A) irritational phenomena consisting of inflammatory cell infiltrations both diffuse and in the form of lymph follicles, edema and vascular engorgement; and (B) glandular changes which consist especially of a transformation of gastric glands into those of the intestinal type, patchy replacement of fundus glands by those of the antral type and microcystic dilatation of the mucous glands. These changes are seldom found to any marked degree in the fundus but tend to grow progressively more marked in the distal part of the stomach with the advance of years. The changes sometimes result in thickening and sometimes in thinning of the gastric mucosa. Although the purely inflammatory exudative features of chronic gastritis probably have a direct relationship with the formation of peptic ulcers as Collins¹ has pointed out, it is doubtful if they have any importance in cancer formation. The glandular changes, on the other hand, may be precancerous for they are apt to be marked in cases of stomach cancer. But rarely, if ever, is it possible to trace a microscopic relationship between the two as Guiss and Stewart² have pointed out and so it remains uncertain whether or not these atrophic changes are definitely precancerous (Stout³). It must also be stressed that carcinoma of the stomach not only develops in just those parts of the stomach where the most marked changes of gastritis are commonly observed, namely along the lesser curvature or adjacent to it in the antrum and pylorus, but it also develops in the fundus and at the cardia where they are very uncommon. Whatever one believes about atrophic gastritis, it is certain that in pernicious anemia in which atrophy of the gastric mucosa occurs to a marked degree, there is a much higher gastric cancer rate than in a comparable age group of the general population; 40 or more times as great according to Rigler and his coworkers.⁴ There can be no question about the fact that atrophic gastritis is present and

often to a marked degree in all but about 6 per cent of stomachs with gastric cancer (Stout³). There is good reason to believe that adenomatous polyps are precancerous growths but again the relationship between hypertrophic gastritis and gastric cancer is less certain. Other factors have been suggested as precancerous lesions. Ewing⁵ mentions congenitally misplaced epithelium in the gastric wall, avitaminosis, and chemical and bacterial toxins, and several authors including Rigler⁴ and Ehrmann⁶ have suggested that hereditary predisposition exercises some influence in the development of gastric cancer but none of these statements has been proved. Whether or not carcinoma may develop from a preëxisting peptic ulcer remains a hotly debated question and the arguments pro and con will not here be rehearsed but there is no doubt about the fact that it is impossible always to distinguish between simple and cancerous ulcers of the stomach by any of the clinical diagnostic methods at our command and the diagnosis can only be reached in some after microscopic study of stained sections. This is a fact of major importance in the treatment of gastric lesions (Allen⁷). In summary it must be admitted that little is known about the etiology of gastric cancer (Ivy⁸).

Carcinoma of the stomach is a neoplasm which is slightly more common in males, it is rarely seen before the beginning of the fifth decade of life, it may develop in any part of the stomach but is commonest in the cephalad half of the distal third. The histological variations of gastric carcinoma are of such slight importance that here they will be ignored. It is, however, of value to know how cancer grows in the stomach and its effect upon gastric morphology and physiology, for diagnosis depends upon the changes produced by it. Carcinoma should be envisaged as originating from a focal point or a group of foci in the mucosa or possibly occasionally from heterotopic epithelial cells in the gastric wall. It tends to grow in all directions, into the lumen, penetrating through the gastric wall and along the gastric wall paralleling its surface. But the rate of growth in one or another direction differs greatly in different cases and this gives rise to the different gross forms observed. If growth is chiefly into the lumen, a fungating tumor results which may sometimes become secondarily excavated by superficial ulceration. If growth is chiefly away from the lumen, penetrating the gastric wall, ulceration occurs almost at once and a shallow bowl-shaped ulcer with little or no elevation of its margins is formed. This is a common cancer type and is responsible for most of the difficulties of differ-

ential diagnosis between benign and malignant ulcers. In a third variety called variously carcinoma in situ (Mallory⁹), slowly progressive mucocerosive cancer (Gutmann et al¹⁰) or 'superficial spreading cancer' (Stout¹¹), the tumor spreads centrifugally in the mucosa and submucosa over a relatively wide area before penetrating deeper into the gastric wall. It usually produces a shallow bowl-shaped ulcer limited to the mucosa and submucosa. There is another much rarer variety of gastric cancer in which there is deep centrifugal spread throughout the stomach wall, thickening and stiffening it but leaving the mucosa uninvolved. This is called linitis plastica or leather bottle stomach. Any one of these varieties of carcinoma may be associated with a chronic peptic ulcer of benign aspect either in the cancer area or in some other part of the stomach. In the last two hundred carcinomas of the stomach resected at the Presbyterian Hospital, 65 were too extensive to permit grouping. The remaining 135 were grouped as follows: penetrating with ulceration 40 per cent; fungating 37 per cent; superficial spreading 20 per cent; linitis plastica 3 per cent. Of the 200, 16 or 8 per cent were associated directly or indirectly with peptic ulcers.

The cancerous growth, no matter what its type, generally interferes with gastric motility over a greater area than is the case with simple peptic ulcer. This is partly because of the scar tissue which accompanies its growth but by no means altogether and it must be confessed that the real reason is unknown. It is also true that in the majority of cases there is a reduction in the secretory activity of the gastric glands which may become achylia; but the reduction does not always occur and there may be actual hyperacidity. Obstruction of the pylorus or cardia because of mechanical blocking by the tumor, muscular hypertrophy or spasm, is a variable factor but generally does not dominate the picture in early neoplasms.

Metastasis from gastric carcinoma is generally early going first to the nodes along the greater and lesser curvatures and later to the liver, lungs and to other lymphatic stations. When it progresses locally outside of the stomach, it invades adjacent organs and structures such as the pancreas, liver, transverse colon, and the mesenteries, omentum and retroperitoneal tissues. It respects the duodenum but not the esophagus and diaphragm. Widespread metastases are not very common.

The only symptoms and signs which will be stressed at this time are the early ones when it may still be possible to cure the patient.

There are two characteristic modes of onset in gastric cancer: (A) After a lifetime of good health a man or woman suddenly begins to suffer from "indigestion consisting usually of epigastric pain or discomfort or a feeling that food is remaining too long in the stomach" (Alvarez;¹² Harris¹³). This may be accompanied by loss of appetite, weight and strength (McVicar and Daly; ¹⁴ Spriggs¹⁵). (B) In a second group the patients have suffered for years with gastric disorders which may be due either to gastritis or peptic ulcer (Usland;¹⁶ Allen;⁷ Palmer¹⁷). Suddenly the character of the symptoms changes and the patient starts to go downhill. Vomiting, pain, occult or obvious bleeding, flatulence and a palpable mass are all late signs which often only appear after the cancer is hopelessly advanced.

Diagnosis is exceedingly difficult in the early stages. The majority of writers feel that examination by x-ray is the most reliable method but even this may fail to detect a very early lesion or differentiate with assurance between a peptic ulcer and an ulcerated cancer. By this method derangements of motility, pyloric obstruction, projecting tumors, ulcerating lesions and changes in the rugae can all be visualized and their significance interpreted with a high degree of accuracy by an experienced radiologist. The reflected images of these same changes can be seen by the gastroscopist although not as completely because there are blind spots which cannot be inspected. With care in performing the analysis and obtaining the specimens, Holman¹⁸ believes that examination of the gastric contents is of great value in differentiating between peptic ulcer and cancer. He found that 100 per cent of patients with peptic ulcers had a normal or elevated secretion of hydrochloric acid and 96 per cent of carcinomas of the stomach had a low acidity or an acidity. Lactic acid in the gastric contents strongly suggests the presence of cancer but does not prove it (Davidson and Calder¹⁹).

All students of the subject, physicians as well as surgeons, are in agreement that the only possible chance of curing gastric cancer is by gastrectomy, while the carcinoma is still confined within the stomach and its immediate removable environs. This means immediate and thorough investigation by x-ray, gastroscopy and chemical analysis of gastric secretions of every individual over forty who complains of a little indigestion which persists without known cause, with frequent repetitions of the examinations, if necessary, and surgical exploration if the symptoms persist and remain unexplained after four weeks treatment.

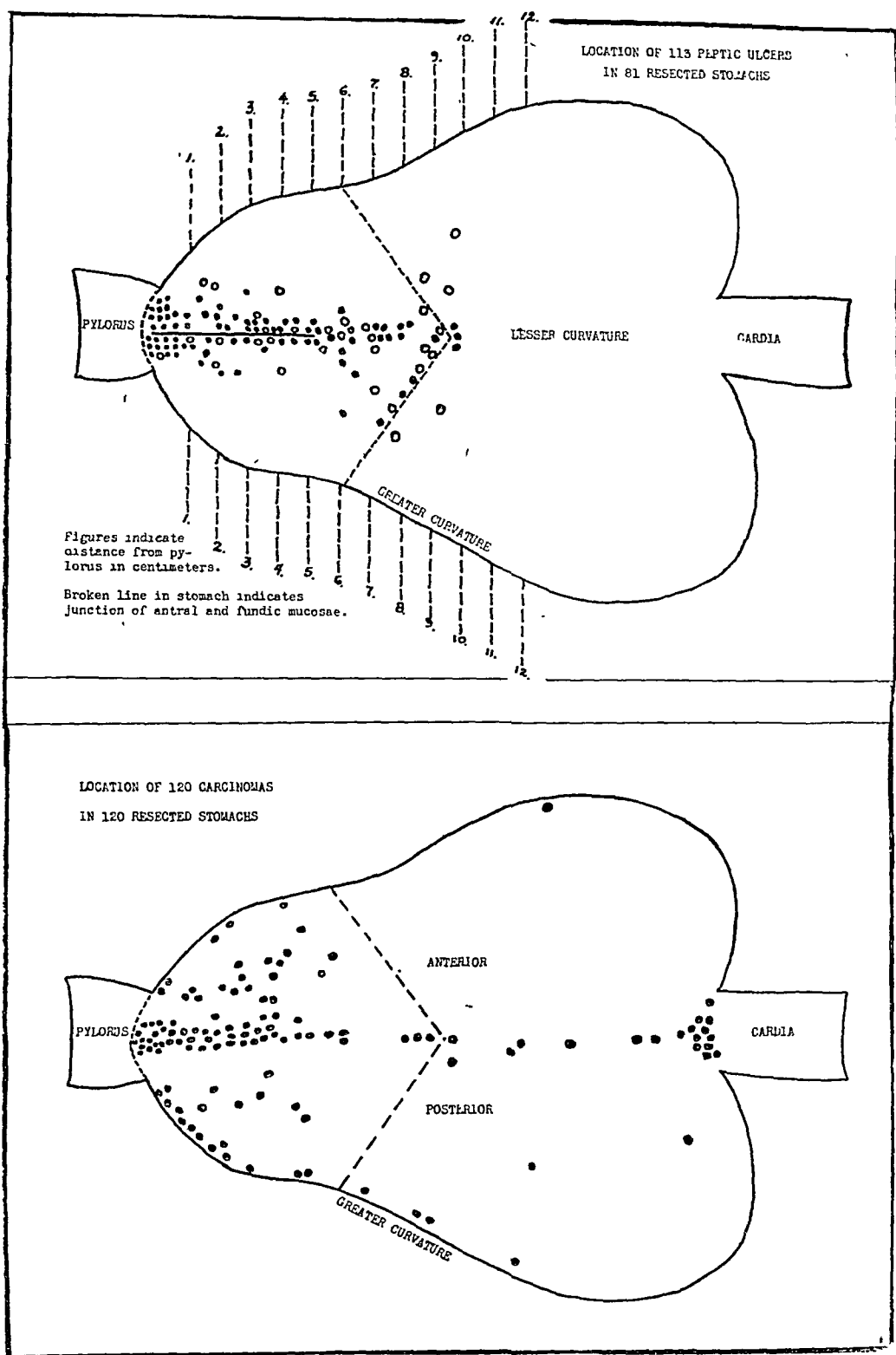


FIG. I

Comparison of the location in the stomach of 115 peptic ulcers and 120 carcinomas. In the diagram the stomach is represented as having been cut open along the greater curvature with the anterior wall above and the pylorus at the left.

It means investigation by the same means of every gastric ulcer which fails to heal progressively and completely after hospitalization and adequate ulcer treatment for four weeks. If with or without an ulcer there is found low acid secretion or achylia, if lactic acid is present, or if there is suspicion of cancer after examination by a competent radiologist and/or gastroscopist, gastric resection should be carried out at once without further delay, for this is good treatment for a simple gastric ulcer and it is the only method by which more early gastric cancers can be cured. Many surgeons consider it mandatory to resect the stomach if an ulcer is over 2 centimeters in diameter because of the relatively high incidence of cancer among large ulcers (Allen⁷). The same advice can be given for all ulcers on the greater curvature and in the fundus because of the extreme rarity of benign peptic ulcers in these situations.

Attempts have been made by St. John, Swenson, and Harvey²⁰ and by Dailey and Miller²¹ to survey large groups of middle-aged and elderly men and women without gastrointestinal symptoms with the hope of discovering and treating unsuspected cancers of the stomach. These show that it is possible to uncover unsuspected gastric neoplasms if individuals are willing to submit themselves to periodic examinations and if experts in diagnosis can be found who are willing to devote a considerable amount of time and effort to the project. Whether or not such examinations can be carried out on a large proportion of the elderly population remains to be seen.

That resection of the stomach is worth while is indicated by the five year cure rate of around 30 per cent of cancerous stomachs removed at the Mayo Clinic (Walters²²). The fact that about one-third of the cancerous stomachs resected at the Presbyterian Hospital were so far advanced that they could not be typed calls attention to the beneficial effects of gastrectomy as a palliative procedure in incurable cases. The remaining months or years of such patients are rendered much more tolerable by ridding them of a foul gastric tumor; pain vanishes, appetite returns, weight and strength increase until recurrences or metastases finally bring the end.

At the present time according to Oughterson,²³ 58 per cent of gastric cancer patients never reach a hospital and in only about 2 per cent of all gastric cancer cases are five year cures effected. There is little doubt that these figures could be improved if more patients could reach the operating table in a curable condition. To accomplish this physicians

must be eternally vigilant for the slight equivocal evidences of early cancer. It is especially important to regard ulcer of the stomach as a serious disease, needing prompt and careful investigation and medical treatment without any procrastination, followed by surgical resection if progress has been unsatisfactory after the elapse of a month. Perhaps most important of all physicians should realize that if they are unwilling to submit their patients for surgical treatment until the clinical diagnosis of carcinoma is manifest, they are causing these unfortunates to lose their only chance of cure.

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THE SURGICAL TREATMENT OF
BONE TUMORS*

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FROM earliest times the surgical treatment of bone tumors has been an established and accepted mode of therapy. That it has held its place up to the present time is an admission of failure on the part of the profession to discover a more ideal method since surgery in many instances implies a mutilating operation. When roentgen-rays and radium were first used in these cases it was hoped that perhaps one or both of these agents might prove the answer to the problem and that surgical procedures, such as amputation and resection, might be relegated to the past and become merely of historical interest. That this has not been the case is a distinct disappointment. In most instances, except when dealing with the benign giant cell tumor and a few of the radiosensitive types of malignant tumors of bone, we have found that the dose of radiation that will destroy or at least permanently inactivate the tumor generally produces irreparable damage to the surrounding normal tissues. Therefore it has been necessary not only to persist in the use of surgical methods but to try to expand them. At the same time surgeons have explored the possibility of substituting for amputation the less drastic procedure of radical resection associated with bone transplants. In selected cases these conservative operations have in many instances proven a satisfactory means of extirpating the primary growth and at the same time saving the limb. Phemister of Chicago was a pioneer in developing this type of conservative surgery. We have utilized it for some years and with increasing confidence that it has a definite place in the treatment of certain types of both malignant and benign tumors of bone.

In the brief time allotted it seems best to outline the indications for surgery in some of the more important tumors of bone, first listing them according to an accepted classification.

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BENIGN TUMORS

Chondroma—Were it not for the fact that certain of the benign tumors not only cause symptoms that require relief but also exhibit a definite tendency to undergo malignant transformation it would often be permissible to leave them untreated. This policy however is not without risk and we have seen a considerable group in which secondary or late sarcomatous development has taken place. This is true both of the central or enchondroma and the osteochondroma, although we have never seen malignant degeneration in chondroma of a phalanx. It is therefore a real responsibility to decide whether or not to employ surgery in a given case. In general the accessible lesions are removed surgically; this is true particularly of the central chondroma. If the decision is not to operate then the patient must be kept under observation for an indefinite period and warned to report at once any change in the size of the tumor or any increase of symptoms.

Clean and complete extirpation of the entire area of involvement is all that is required. Central chondromas may be carefully curetted and the resulting cavity then treated with an escharotic, such as zinc chloride, following which it may be filled with bone taken from the ilium or the tibia. Osteochondromas should be removed completely leaving a base of normal bone. Incomplete removal is hazardous. Chondromas of the pelvic bones constitute a distinct problem due to the difficulty of complete extirpation.

Bone Cyst and Giant Cell Tumor—These two conditions are considered together not only because they have many features in common but because their surgical management is essentially the same. Thorough curettage through a window wide enough to give good exposure and adequate access to all parts of the tumor is usually curative. However bone regeneration in the destroyed area is facilitated and made more certain if transplants of strips of cortical bone from the tibia, or chips of cancellous bone from the iliac crest are used to fill the cavity. Here also an escharotic solution is generally used to swab the lining of the cavity prior to closure of the wound in layers without drainage or packing. Primary wound closure as we have often emphasized is a matter of paramount importance. Giant cell tumors located in the rib, fibula, or patella may be dealt with by resection of the entire tumor-bearing area with assurance against recurrence. In the upper tibia and

lower femur, where the majority of these tumors are found, curettage may in 10 or 15 per cent of cases be followed by a recurrence. In some of these cases a second curettage is essential but in others, due to an accompanying change in the cellularity of the tissue, successive attempts at removal are unsuccessful and end with a definite sarcomatous alteration. In such cases even amputation may fail to prevent death from pulmonary metastasis. Fortunately these tragic consequences are infrequent nor are they confined to cases managed by surgery but at times may follow roentgen therapy. Solitary bone cyst responds more uniformly to curettage than does giant cell tumor; recurrences are less frequent and less serious since most of them yield to a second curettage; we have yet to see an example of late malignant transformation in a case treated by surgery alone. However, we have records of three instances of sarcoma developing from 13 to 15 years after roentgen therapy.

MALIGNANT TUMORS

Osteogenic Sarcoma: By far the greater proportion of cases of osteogenic sarcoma of long bones offers little or no opportunity for conservative surgery and amputation is admittedly the only course open to the surgeon. Inasmuch as the average practitioner sees so few of these cases he is apt to accept the pessimistic views of those who contend that amputation is nearly always followed by a fatal outcome. I am opposed to this defeatist attitude and wish to express a different view.

In a series of histologically confirmed cases treated at Memorial Hospital from 1917 to 1940 the survival rate for osteogenic sarcoma was 21.8 per cent. We have records of 56 patients who have survived for five or more years and only five of them died subsequently of sarcoma. Of these 56 patients 16 were well for more than ten years. Moreover considering only those cases regarded as suitable for amputation, Pool and I found the five-year survival rate in a series of 89 amputations to be 32 per cent. This would seem a worthwhile salvage in a disease that is regarded by some to be nearly always fatal.

It has been stated that amputation for osteogenic sarcoma ought always to be performed proximal to the bone involved rather than through it. This rule seems at first glance entirely logical but it involves a hip-joint disarticulation in cases of sarcoma of the lower femur which, incidentally, is the most frequent site of the disease. In our experience

few patients have been able to get about with any degree of satisfaction using a hip-joint prosthesis. Therefore for the past twenty years we have been practicing high thigh amputation in cases in which the character and extent of the tumor seemed to warrant it. Our results prompt us to recommend it as a substitute for routine disarticulation at the hip in cases in which clinical and roentgenographic examination show the tumor to be confined to the lower third of the femur. The level of amputation in such cases varies but it is always at least as high as the junction of the upper fourth and lower three-fourths of the bone.

In order to ascertain the risk involved in amputating through the affected bone rather than proximal thereto a survey was made of 40 consecutive cases in which this procedure was adopted. In 39 cases the lesion involved the lower femur and in one, the lower fibula. Stump-recurrence took place in only two instances or in 5 per cent, but in one of these a secondary hip disarticulation was followed by a five-year survival. Hence it is assumed that a hip disarticulation was avoided in 38 cases only to have one in which such a procedure might perhaps have succeeded. The five-year survival rate in these 40 cases was 14 or 35 per cent. This is slightly better than the figure reported by Pool and myself for 89 unselected amputations. This survey seems to offer conclusive evidence that, with due regard to the selection of cases, the principle of avoiding the more mutilating operation of hip-joint disarticulation is a sound one.

In exceptional circumstances a less radical procedure than amputation may be attempted. For selected cases of chondrosarcoma of the scapula a total scapulectomy is as satisfactory as is an interscapulo-thoracic disarticulation and it preserves a useful upper extremity. Segmental resection of the tumor-bearing area of a long bone supplemented by massive bone graft is a valuable means of avoiding amputation; this method may be used more extensively as our experience with it increases. Phemister has even resected a segment of the femur for central sarcoma and substituted therefor grafts from both tibiae with an excellent result.

Endothelioma—Ewing's Sarcoma of Bone: The widely held belief that Ewing's sarcoma of bone (endothelioma) is highly radiosensitive is probably based upon the prompt relief of pain and disappearance of the swelling followed by reparative changes in the bone which accompany even small doses of roentgen therapy. However, Woodard and

I have found that results are quite variable for long-term control of the local lesion. We feel that tissue doses as high as from 3000 to 5000 r can be expected to control the growth in about 50 per cent of these cases, and that doses in excess of 6000 r may be required to sterilize the tumor permanently. Such huge doses can be expected to cause complete loss of the normal regenerative powers of bone.

We believe therefore that it is worthwhile in cases with a favorable setting to attempt a resection of the tumor-bearing portion of the bone after a moderate course of preliminary radiation. We have several patients who have survived for long periods following the employment of this method. Unfortunately opportunities to utilize this combined attack are not often encountered.

It is our opinion that before resorting to any form of treatment for Ewing's sarcoma, a microscopic diagnosis should be made since even small doses of roentgen-rays may so alter the histologic appearance of the disease as to prevent the pathologist from identifying the tissue subsequently removed as *endothelioma*. In such instances, a diagnosis of "inflammatory process" is usually rendered and treatment is either suspended entirely or is undertaken with the misconception that one is dealing with an infection rather than a sarcoma.

Plasma Cell Myeloma: This uniformly fatal disease offers few opportunities for surgical treatment because of its polyostotic distribution. Aspiration biopsy is generally a satisfactory substitute for open biopsy. However if for any reason, aspiration is not considered advisable, surgical biopsy is applicable.

Reticulum Cell Sarcoma Primary in Bone: Since Parker and Jackson first described this tumor in 1939 we have encountered only 11 cases which seemed to fulfill the necessary criteria. We would emphasize that while histologically there is a close resemblance to Ewing's sarcoma the roentgenographic appearance is not typical of the latter disease. The tumor is radiosensitive and our experience leads us to regard radiation therapy as the method of choice. Amputation can usually be avoided; therefore when a surgical biopsy results in a definite diagnosis of reticulum cell sarcoma it is proper to regard further surgery as seldom indicated.

Liposarcoma of Bone: There is as yet no widespread acceptance of the theory that primary liposarcoma of bone is a definite entity. Long survival after amputation in a few cases in which this diagnosis has been

made, however, prompts us to recommend it as an appropriate method of treatment. There is some evidence however that these extremely rare tumors are radiosensitive.

Palliative surgery for metastatic tumors of bone and inoperable sarcoma: It is well to recognize the fact that bone metastasis from cancer primary in other organs constitutes a numerically greater proportion of all skeletal malignant disease than does any of the bone sarcomas. Among the cancers which have a predilection for osseous involvement the following predominate: breast, prostate, kidney, thyroid and lung. It has been found impossible to effect a cure once bone metastasis has occurred. This being the case there is little place for surgery in the treatment of these unfortunate patients. Occasionally one encounters a case with marked involvement of a major long bone which histologically has been established as metastatic cancer and yet a painstaking search has failed to disclose the primary tumor or any other evidence of metastasis elsewhere, and the general health of the patient is excellent. This situation poses a problem in choice of treatment. One may elect to irradiate the part or to perform an amputation. If the pain is severe and a pathologic fracture is impending then removal of the limb may be followed in some instances by a long period of wellbeing and comfort. Before resorting to amputation in such cases it is imperative to obtain roentgenograms of the entire skeleton and to examine the patient thoroughly in the hope of discovering a primary growth. We have a few cases of palliative amputation in which the result obtained seems to have justified the procedure.

We are even more strongly convinced that patients with painful primary sarcomas, especially of the osteogenic and chondrosarcoma types, are made much more comfortable when, despite the presence of demonstrable metastatic lesions in the lungs, the offending member is amputated. This is a humane procedure.

Among the most difficult cases to manage are those with bulky, slowly-growing tumors of the pelvic bones. These radioresistant lesions include the chondromyxosarcomas and the sacral chordomas which seldom terminate in early metastasis but which wear the patient down by the effects of constant, excruciating pain. In such situations any form of radical surgery that offers the slightest prospect of eradication of the disease is justifiable; this includes even hemipelvectomy. Where no form of surgical extirpation is possible we have found that spinothalamic

cordotomy has given a large measure of relief providing it has been performed before the patient has had opiates. The latter counteract the beneficent effects of the surgical procedure by leading to demoralization which may ultimately cause the patient and his family as great distress as the pain itself.

SUMMARY

Benign tumors of bone require surgical treatment not only for the present symptoms but for future malignant potentialities. The form of therapy differs with the type, the extent and the location of the tumor but seldom should amputation be required.

Surgery is also indicated for malignant tumors of bone. This implies amputation in most instances particularly for those types that are radio-resistant.

High thigh amputation for tumors of the lower femur has proved an acceptable substitute for routine hip-joint disarticulation. For tumors in other situations, amputation proximal to the bone involved is generally advisable although exceptions exist.

Under certain conditions and in special locations malignant tumors may be dealt with successfully by conservative surgical measures such as local excision, resection, curettage, scapulectomy, patellectomy, etc., rather than by amputation.

Judgment born of experience is of inestimable value in the selection of the method of treatment best adapted to the individual case.

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EMANUEL LIBMAN

1872-1946

Dr. Emanuel Libman passed away at the Mount Sinai Hospital on June 28, 1946, after a brief illness. Throughout his professional career he had devoted himself whole-heartedly to medical science and research, to medical practice of a high order, to the study of medical literature, to medical education and to promoting in others those ideals which had inspired his own life.

Libman was born on August 22, 1872, in New York City; he was graduated from the College of the City of New York with the degree of A.B. in 1891, and from the College of Physicians and Surgeons of Columbia University in 1894. During his internship at the Mount Sinai Hospital he came under the influence of Dr. Abraham Jacobi and Dr. Henry Koplik, and at first planned to become a pediatrician. With this in mind he made a trip to Europe and studied bacteriology in Graz under Theodore Escherich who had discovered the colon bacillus. In only a few weeks' work in Professor Escherich's laboratory, he discovered the *Streptococcus enteritis*, and isolated this streptococcus from the patient's blood. This initial experimental research may account for Libman's subsequent extensive work in blood cultures, in the "General Infections," and in bacterial endocarditis. On his return to New York he was appointed assistant pathologist at the Mount Sinai Hospital, and from that time played a most important and vital role in the development of its laboratories, both routine and research.

In medical history his name will probably always be associated with endocarditis in general, with the bacteria-free stage of endocarditis and with his description with Dr. Benjamin Sacks of a new form of endocarditis which he called atypical verrucous endocarditis, now termed the Libman-Sacks disease.

Notable as were his achievements in bacteriology and pathology, he will be remembered by many physicians for his extraordinary knowledge of internal medicine

and its literature, and his brilliance as a diagnostician. He had come under the influence of three great internists, Dr. Francis Delafield, Dr. Edward Gamaliel Janeway and Dr. William Osler, and at least some of his success was due to their fine example and teaching.

Important as his work was in the laboratory and at the bedside, of equal value were his interest and promotion of postgraduate medical education of others, especially of younger physicians. The outstanding characteristic of Libman was his ability to stimulate, to inspire, to quicken others to work and study with something of his own enthusiasm. He was instrumental in getting the initial funds for the work of the Committee on Medical Education at his hospital. He either himself endowed or helped in the establishment of the following funds, all for medical education or research:—the Edward Gamaliel Janeway Lectureship, the William Henry Welch Lectureship, a lectureship in honor of Hideyo Noguchi at the Johns Hopkins Hospital, the Humphrey Davy Rolleston Lectureship at The Royal College of Physicians in London, the Herbert Celler Fellowship Fund, and the Henry Dazian Foundation for Medical Research. The latter during the recent war provided fellowships for Latin-American doctors wishing to pursue research in this country. He was a great friend of, and liberal contributor to the Hebrew University in Palestine. It is not so well known that he left a contingent legacy in his will for the Tuskegee Institute of Alabama, probably as an expression of his own belief that "mankind should treat all races as one." The Libman Fellowship Fund was established by a number of his friends as a tribute to Libman for his work in postgraduate medical education.

He always enjoyed working at the Academy of Medicine. He was a leading spirit in the activities of the Committee on Medical Education of The New York Academy of Medicine from its incipency to the last

year of his life when he reluctantly withdrew because of his failing health. The Graduate Fortnights, originally suggested by Dr. Ludwig Kast, were always a challenge to him, and their success year after year was a source of great satisfaction, as he considered them a valuable means of teaching. He was one of the first, if not the first to form a group who demonstrated exhibits over and over again to successive audiences. The most perfect tribute to Libman, but necessarily incomplete, is the "Introduction" to the three Libman Anniversary Volumes, by his great friend, William H. Welch. In that introduction Dr. Welch writes: "An almost unsurpassed gift of Libman as a teacher is his skill in collecting material and in preparing exhibits of specimens and illustrations for his lectures and demonstrations. Many of his appearances, accompanied often by a group of his pupils to present a paper or exhibit at a meeting of medical societies or at international congresses have been notable events, never forgotten by the hearers. I doubt if there has ever before been assembled such an instructive and comprehensive exhibit of the cardiovascular system in all its aspects, ana-

tomical, physiological, pathological, bacteriological and clinical, as that brought together under the supervision of Libman to illustrate the course of lectures and demonstrations of the Graduate Fortnight of the New York Academy of Medicine in October, 1931.

In addition to his formal work in medical education, he was tireless in his efforts to help younger physicians and scientists by his sound advice, his stimulation and his financial aid. As a result he built up a school of disciples and gathered a host of personal friends both here and abroad with whom he kept in touch to the end of his life.

Libman belonged to an age which is passing, but he saw clearly the age that is waiting before, and prepared others to meet the burden of the future. He was a scholar, an investigator, a fine physician and a philanthropist. He preached and practised the continued education of the physician throughout his own long and brilliant career in medicine. We who knew him will always cherish his memory.

BERNARD S. OPPENHEIMER.

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CRITICAL EVALUATION OF THE USES AND DANGERS OF TRANSFUSIONS

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RECENT ADVANCES IN THE TREATMENT OF LYMPHOMAS AND LEUKEMIAS

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BACK PAIN OF NERVOUS ORIGIN

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BACK PAIN OF PSYCHOSOMATIC ORIGIN

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BULLETIN OF THE NEW YORK

ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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1947

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MARCH 1947

CENTENNIAL CELEBRATION

1847 — 1947

As The New York Academy of Medicine enters its second century of service to the medical profession and to the public, it will review the achievements of its stalwarts of the past and Janus-like, look forward with eager eyes to the opportunities and problems which will confront this changing world. The strength of the Academy has developed from a twofold source—its men and its forthright attitude and purpose. Its men have been strong and its purpose that of service and leadership.

The programs of the Sections will exemplify this bifocal function of the Centennial Celebration and it is hoped that, aside from addresses on specific techniques or problems in medicine, the members of the Sections will grasp this opportunity to survey the past and look into the immediate future in the various fields of medicine, surgery, and psychiatry.

A glance at the programs for the Institutes on Social Medicine, Public Health, and Medical Education suggests the interest and the responsibilities of the Academy in some of the broader fields of medical activity, fields often touched by the individual physician only with difficulty, and only if he is minded that way. These Institutes will be working conferences devoted to the subjects indicated and led by acknowledged leaders in the respective fields. The Institutes will be conducted informally and should prove to be both expository and pro-

cancer. A man of high idealism and great good will like James Ewing could carry on what amounted to a crusade for radiation. This wave of enthusiasm for radiation led to its use for all types of neoplasms, and the evolution of many ingenious methods of applying it.

Unfortunately, these high hopes of a generation ago in the curative value of radiation were dissipated as knowledge of its effects accumulated and the end results became available.

Today it is clear that except for a few types of cancer such as some forms of epithelioma of the skin, epithelioma of the larynx, and epithelioma of the cervix, radiation can not compete with surgery as a curative agent. This period of disillusionment in the curative value of radiation carried us into the 1930's, and the period preceding the recent war.

Although our experiments with radiation left many of us chastened, they taught us important lessons. First, they revealed the great usefulness of radiation as a palliative form of treatment. From this palliative standpoint alone radiation has won for itself an important and lasting place among the weapons which every properly equipped hospital must possess. Trained radiotherapeutists are an essential part of any organization attempting to treat cancer today. Radiation checks temporarily several types of malignant disease in which surgery is futile. Lymphoblastomas and the highly malignant epitheliomas of the posterior tongue and pharynx are examples. It brings relief to many suffering with metastases from breast cancer.

A second gain from our period of enthusiasm for radiation has been the development of specialization in cancer. It is a historical fact that the cancer clinics in which radiotherapy evolved, the Radium Institute in Paris, the Radiumhemmet in Stockholm, and our Memorial Hospital, have also become the leading centers for training specialists in cancer diagnosis and treatment. James Ewing was a firm believer in specialization in cancer and we can thank him for what progress has been made in gaining recognition for our specialty in this country.

As with most other modern complex fields of knowledge, specialization in cancer has been fruitful. It has led to improved diagnosis and more expert care of the patient. The public and a large section of the medical profession are well aware of this fact, and cancer hospitals and cancer clinics are handling a constantly increasing share of the cancer patients.

Despite all this the medical schools and teaching hospitals have not given our specialty much recognition. The academic mind continues to resist new forms of specialization despite the fact that the rapidly increasing complexity of modern science makes specialization as inevitable as tomorrow's sunrise. In any good hospital clinic on any day one sees a wide variety of specialists excelling in their knowledge of the diseases in which they are specially interested. A man who spends the mature years of his life studying one disease naturally comes to know more about it than his colleagues who dissipate their efforts. If he happens to be an able technician he develops a superior surgical technique. But his technical skill is the least important of his advantages. If he has had a broad general training before specializing, and if he is a man of intelligence, he will draw upon knowledge from the fundamental sciences and from every field of medicine and surgery and apply it in his intensive study of the disease in which he specializes. It is not just to stigmatize such a man as a narrow specialist in technique.

Although the traditional conservative point of view that the general surgeon can treat the various types of cancer equally well still prevails in academic circles, there are signs of a beginning awareness of the advantages of a degree of specialization in cancer. It is becoming apparent that the surgeon who excels in abdominal surgery and is of necessity an expert in gastrointestinal physiology, may treat cancer of the stomach and bowel with great skill; yet he may not do as well with the tedious and radical dissections required for cancer occurring elsewhere in the body, for example in the mammary gland, where a knowledge of pathology is more fundamental. There is need for all our skills in dealing with such a formidable enemy as cancer, and no one man can encompass them all. Let us by all means aim first at what is best for the patient and forget tradition.

To continue our historical review we come to the present trend in cancer therapy. It might be called the surgical epoch. During the last ten or fifteen years advances in certain of the fundamental aspects of surgery have made it so much safer that it is today possible to attack cancer far more vigorously. Improved anesthesia today permits the surgeon to operate for a far longer period of time without excessive shock. Operating on the surface of the body we can work comfortably for five or six hours. This permits us to do much more thorough and better dissections. It is fair to say that this improvement in anesthesia

has been the most important single factor in the recent rapid development of thoracic surgery and the attack on lung cancer.

The improved facilities for blood transfusion have also been of much assistance to the surgeon in his attack on cancer, for they have certainly lowered the mortality from operative shock.

The abdominal surgeon has found a strong defence against his old enemy, intestinal obstruction, in the use of the Abbott tube. Abbott is gone, struck down himself by malignant disease, but his discovery is saving lives every day of patients who have had gastric or bowel resections for cancer.

The frequency of local recurrence following many types of operations for cancer that have been done in the past can leave no doubt about the desirability of surgeons taking advantage of their newly found technical advantages. Our course, indeed, is clear. In many forms of cancer where radiation has failed to cure or has given only a limited percentage of cures, and where a more radical surgical attack is possible, we must have the courage to develop it, no matter how mutilating it may be. This, we might say, is our present temper.

The surgeon who today faces the grave responsibility of carrying out a mutilating operation for cancer has one solid advantage over his predecessor of Dr. Halsted's era: he has the surgical pathologist by his side to assist him in making certain of the diagnosis and to advise him as to the extent of the dissection. Fifty years ago surgical pathologists did not exist and the frozen section method of making an immediate microscopic diagnosis had not been developed. It was, in fact, in 1905 that Wilson of the Mayo Clinic began to use it. Dr. Halsted and his contemporaries had to depend upon their clinical impressions and their knowledge of gross pathology in diagnosis. We know that every now and then, particularly for lesions of the mammary gland, these evidences are delusive. Dr. Bloodgood, as a matter of fact, once wrote in an account of his early days in Halsted's clinic that 10 per cent of the benign lesions of the breast were mistaken for carcinoma and radical mastectomy needlessly done.

Thanks to the methods of immediate microscopical diagnosis which surgical pathologists have since perfected, this kind of mistake need never occur today. The frozen section method of diagnosis is the one which Dr. Stout and I have found to be the most desirable, and we have no evidence that the careful excision for frozen section of a tiny

wedge of tissue measuring only a few millimeters in size, from the superficial aspect of the lesion, is harmful. Others prefer the aspiration method of diagnosis. No matter which method is used the surgical pathologist has rescued us surgeons from the sea of doubt and set our feet on solid ground.

Equally important is the fact that the surgical pathologist is our guide in planning the extent and the nature of our attack on cancer. His microscope is a measure of how it extends and metastasizes. A great many patients come for treatment so late that their lesions are inoperable, or to put it another way, surgery will do more harm than good. This decision depends primarily upon a knowledge of surgical pathology.

At Columbia, A. P. Stout, as surgical pathologist, Maurice Lenz, as radiotherapist, and John Hanford and I as surgeons, have formed a team in attacking cancer. We see the patients together in the outpatient Neoplasm Clinic, and advise regarding problems arising on the wards and in the operating room. We keep special records of certain types of cancer cases, and from time to time review our therapeutic results. In this kind of team each member must know a good deal about the other's specialty, if there is to be a genuine meeting of minds. The surgical pathologist should have been trained in clinical surgery, and the surgeons and the radiotherapists should have had an apprenticeship in surgical pathology.

There is today in this country a great shortage of surgical pathologists and of funds with which to pay them. They are keymen in a cancer clinic. Surgeons and radiotherapists gain their income from private practice, but the surgical pathologist is traditionally an employee of the hospital in which he serves, and his salary is notoriously inadequate. Hospitals in which there is no surgical teaching tend to skimp or do without pathology. Men of ambition and talent will be attracted to the specialty only when there is promise of better salaries. If I were asked today what single kind of subsidy on the part of the Federal government would do the most to improve cancer therapy throughout the country, I would say "A fund providing fellowships to train surgical pathologists, and adequate salaries for men properly trained in the specialty, in key hospitals in every community." The cancer clinics which are springing up everywhere now-a-days would be tremendously helped by this kind of subsidy for surgical pathologists.

CANCER
 AVERAGE ANNUAL INCIDENCE RATES PER 100,000 POPULATION
 NEW YORK STATE, EXCLUSIVE OF NEW YORK CITY
 1942-1943-1944

ORDER OF INCIDENCE	SITE	SEX	ANNUAL INCIDENCE
1	BREAST	FEMALE	60.0
2	CERVIX UTERI	FEMALE	34.3
3	SKIN	MALE	29.2
4	STOMACH	MALE	27.1
5	COLON	FEMALE	24.4
6	PROSTATE	MALE	23.2
7	SKIN	FEMALE	19.8
8	COLON	MALE	19.6
9	STOMACH	FEMALE	17.6
10	RECTUM & RECTOSIGMOID	MALE	15.2
11	LUNG	MALE	14.7
12	OVARY	FEMALE	12.2
13	RECTUM & RECTOSIGMOID	FEMALE	12.1
14	FUNDUS UTERI	FEMALE	11.9
15	BLADDER	MALE	11.5
16	LIP	MALE	6.8
17	LEUKEMIA	MALE	6.3
18	PANCREAS	MALE	5.7
19	LIVER	FEMALE	5.5
20	BLADDER	FEMALE	5.2

ALL SITES FEMALE - 270.8

ALL SITES MALE - 231.8

TABLE I

Having reviewed the general trend of cancer therapy it is of interest to speak briefly of the current view regarding the treatment of the most frequent special types of malignant disease, illustrating, as we go along, some of the general conclusions that we have drawn.

I should like first to call your attention to Table I which shows in graphic form the recent morbidity data for cancer in New York State compiled by Dr. Morton Levin of the State Department of Cancer Control. These data are unique, I believe. They have been collected with great care from hospitals, doctors, and public health agencies. They provide, for the first time, a fairly accurate picture of the true comparative incidence of the various types of cancer. This order of incidence is rather different than the impression which those of us who work entirely in hospitals have had. Cancer of the breast is by far the most frequent type, being almost twice as common as any other form of cancer. Cancer of the cervix is next in order, followed by cancer of the skin in males. Cancer of the stomach in males is fourth in order. Cancer of the colon in females is fifth, cancer of the prostate is sixth in order. Cancer of the skin in females is seventh. Cancer of the colon in males is eighth. Cancer of the stomach in females is ninth. Cancer

of the rectum and rectosigmoid in males is tenth. Cancer of the lung, which appears to be the only form of cancer that is actually increasing, is far more common in males than in females, and in our chart it is eleventh in order. Cancer of the ovary is twelfth. Cancer of the rectum and rectosigmoid in females is thirteenth, and cancer of the fundus of the uterus is fourteenth. Cancer of the bladder in males is fifteenth. The remaining forms of cancer are considerably less frequent, and need not occupy us here.

CANCER OF THE BREAST

Cancer of the breast presents a diagnostic problem that requires expert clinical and pathological judgment. The public has been pretty well convinced that a tumor in the breast requires surgical investigation. Not so all doctors. There is appalling evidence that our medical education is not fitting physicians to meet this diagnostic problem. In a series of cases which we have recently studied from the viewpoint of who was responsible for the delay in diagnosis we found that the patient was to blame in 63 per cent of the cases, but some physician was to blame in 27 per cent. These cases are all ones in which the patient had discovered her own tumor and went for advice concerning it. She was told that it was harmless, or given some kind of placebo, or told to return for re-examination at a distant date. She was *not* told that she might have a cancer and that she must enter a hospital promptly for diagnosis and treatment. In this series of patients the consequent delay between the time the patient received the bad medical advice and the time correct treatment was begun averaged 59.6 weeks. We know that a delay of more than six months in cancer of the breast cuts the cure rate in half.

These facts force us to conclude that the most important thing that we can do to improve results in cancer of the breast is to pound into our students and interns the simple and fundamental rule that any tumor of the breast, no matter how innocuous it may seem to be, must be regarded as possibly being a carcinoma. The patient should be admitted to a hospital promptly, all preparations made for a radical mastectomy, and the nature of the lesion proved microscopically. It would appear that we are more in need of education of physicians than of the public in cancer diagnosis. One would like to see the funds recently subscribed by the public for cancer control devoted to providing

graduate training for physicians rather than for propaganda to the public.

Cancer of the breast is one of the types of cancer in which radiation has been extensively tested. About ten years ago we carried out a clinical experiment with radiation in this disease which has given us evidence that has led us to conclusions which are fundamental for us. A series of patients with operable and borderline carcinomas were treated intensively with radiation by Dr. Lenz. The total amount of radiation given to these cases was in general as large as the modern divided dose technique permitted. Several months were required to complete it. After a suitable delay to permit recovery from the acute radiation reaction radical mastectomy was done. In every one of these cases careful microscopical study of the specimen revealed persisting carcinoma cells. These cells usually show signs of having been severely injured by the radiation, and they lie locked up in a dense fibrous stroma. We assume, however, that they are alive and capable of renewed growth. Clinical experience supports this assumption, for we have repeatedly seen carcinomas of the breast that regressed initially following intensive radiation, remained quiescent for two, three, four, or even five years, and then began to grow again. These facts have led us to conclude that radiation will not *cure* carcinoma of the breast, and we have given it up in the disease except as a palliative agent. We do not use it prophylactically as an aid to surgery because operation alone is highly efficient in controlling the local disease, and we have no reason to believe that radiation to the operative field has any effect upon the incidence of distant metastases, our *bête noir* in breast cancer.

Having been forced by the failure of radiation to rely for *cure* entirely upon radical mastectomy we have attempted to use the operation more critically. Dr. Stout and I have recently worked out criteria of operability. We have found that there are certain types of breast carcinoma that are never cured by surgery. These include the inflammatory type of breast cancer, cases with extensive edema of the skin of the breast, and most cases in which the tumor is solidly fixed to the chest wall. We believe that operation in these cases not only fails to cure but actually shortens life by hastening metastases. In these inoperable cases radiation is the preferred method of treatment, and Dr. Lenz has sometimes succeeded in arresting the disease for as long as five years.

Where breast cancer is operable we believe in performing the

most radical operation that can be done. With modern surgical technique we have been able to extend the original Halsted operation. We remove so much tissue that a large Thiersch graft is required to cover the defect on the chest wall. Our operation requires 5 or 6 hours to carry out, but when done with proper care it has a negligible mortality and it does not cripple the arm. Comparisons in our own hospital indicate that this truly radical operation gives only half as many local recurrences, and a 50 per cent higher five-year cure rate than the usual so-called radical mastectomy. This improvement is no doubt due in part to our more critical selection of cases for operation.

These, we believe, are our best hopes for improving the results with carcinoma of the breast. In younger women sterilization, and in older women the administration of estrogens or androgens, occasionally check the progress of bone metastases temporarily, and in rare cases have been known to retard the advance of the primary tumor. These hormonal agencies, however, are not to be regarded as of much practical importance in the control of breast cancer. Their effects are too inconsistent and too feeble to make them rivals of radiotherapy. When they are used as supplements to radiation it is difficult to assess their real value.

CANCER OF THE CERVIX

Carcinoma of the cervix has slightly more than one-half the frequency of breast carcinoma. From the causative standpoint there is one remarkable feature about the disease that gives hope that its incidence can be cut down. This is the fact emphasized by Twombly, that cervix cancer is extraordinarily rare among Jewish women whose husbands have been circumcised. We know also that it is a disease of the under-privileged among whom baths are not in general as available as among the well-to-do. These facts strongly suggest that improved hygiene and a rising standard of living may appreciably reduce the incidence of the disease.

As to diagnosis, we face the problem of educating patients to submit to examination, and of training physicians to do proper vaginal examinations. The disease is often missed simply because examination of the cervix is omitted.

In the overwhelming majority of cases its presence is obvious if the cervix is carefully inspected. A biopsy with a simple biting forceps

suffices to prove the diagnosis. Papanicolaou's method of making the diagnosis from smears may eventually come to be valued as a quick method of singling out suspicious cases for more careful study.

Carcinoma of the cervix is, of course, the one disease in which radiation has become the preferred method of treatment. When used expertly about 35 per cent of five year cures can be obtained with it. The reasons for this comparative success of radiation are obvious. The cervix, being a small hollow organ, can be attacked with radiation both from within and from without. The radiation effect which results is intense, and without doubt completely destroys the carcinoma in many cases.

In keeping with the contemporary general trend toward surgery in the treatment of cancer, the radical surgical attack on carcinoma of the cervix has recently been revived by Meigs in Boston. Taylor and Twombly in our own city have also begun to do the Wertheim operation. They perform it on alternate cases and thus can compare its results with radiation. It is significant of the progress of surgical technique that the lowest mortality that Wertheim himself was able to report in 1911, when he had brought his operation to the peak of perfection for his day, was 15 per cent. Meigs and Taylor and Twombly, however, with our modern technical resources have performed the operation in more than a hundred cases without any operative mortality. The great handicap of the Wertheim operation, of course, is that it can be done only in the comparatively early cases, and these constitute only a limited percentage of all those who come for treatment. It is too soon yet to draw any conclusions as to the usefulness of the operation in comparison with radiation.

We can not leave the subject of cancer of the cervix without mentioning the fact that we owe our modern standards for reporting the results of cancer treatment to the European gynecologists. In 1928, under the Cancer Commission of the League of Nations, they drew up a set of rules specifying the data necessary for statistical purposes in reports of cancer treatment. A special point was that no deductions were to be allowed for patients incompletely treated, for those lost track of after treatment, and for those dying of intercurrent disease within the five year period. If this rule were followed by all who report the results of cancer treatment we would today have a great deal more accurate data for comparison of different therapeutic methods.

CANCER OF THE SKIN

Cancer of the skin is today treated in most clinics with radium or x-rays, under the direction of dermatologists or radiologists. Despite the fact that patients with skin cancer usually come for treatment while the disease is limited in extent, and despite its accessibility, a good many recurrences result following radiation as it is generally employed, and we see all too many tragic cases in which very radical and mutilating surgery has finally to be done. Dr. Stout and I, after seeing the comparative results of surgery and radiation, have come to believe that in most instances it is better to attack the disease surgically in the beginning. Our reasons for this can be summed up under three heads.

1. Surgery incapacitates the patient for a shorter time and is therefore more economical. A surgical wound is healed in a week while a radiation reaction persists for a month.

2. Surgery gives a better cosmetic result than radiation. Scars made with modern surgical technique are almost invisible, while the scar resulting from adequate radiation is a depressed white, telangiectatic, easily traumatized area of skin.

3. Surgery is more certain to cure. With the surgical techniques that the plastic surgeons have developed during the last twenty-five years it is possible to excise comparatively large areas of skin and sub-jacent tissues and to repair the defect by shifting flaps or transplanting skin. This ability to sacrifice tissues generously gives the surgeon an advantage over the radiotherapist, who usually limits his field closely around the lesion. The radiotherapist, moreover, is at a great disadvantage where the lesion overlies bone or cartilage, for radiotherapy is not successful with epithelioma involving these structures. Finally, when surgical excision is done it is possible for the surgical pathologist to study the depth and extent of the epithelioma in the specimen, and to give the surgeon an accurate estimate of the thoroughness of removal. The radiotherapist lacks any such guide, and his treatment is necessarily less exact and more empirical.

An exception to the assignment of skin cancers to the surgeon should be made for skin cancers occurring in the aged and feeble, in whom radiation is preferable.

CANCER OF THE STOMACH

Cancer of the stomach, the fourth most frequent type of cancer,

is a silent enemy that gives no warning of its presence until it is inoperable in the overwhelming majority of patients. Our problem with the disease is a diagnostic one: gastric resection aiming at cure can be done in only about 15 per cent of those who come for treatment. We must find a better method of detecting its presence in an operable stage if we are to make any headway against it.

Gastroscopy is helpful in some cases, but x-ray study is the most reliable method of diagnosis. Its great disadvantage is its expense. In New York today a gastrointestinal series costs from \$60 to \$75. Oftentimes patients with vague digestive disturbances, over the age of 50, in whom the presence of the disease should be suspected cannot afford such an expensive diagnostic procedure, and it is omitted.

Many patients with cancer of the stomach have no symptoms at all until the disease reaches the inoperable stage. In an effort to pick up these silent lesions, Dr. Paul Swenson, lately of our Clinic, and now at Jefferson Medical School, studied a series of 2413 patients who had no digestive symptoms of appreciable significance. He made a rapid fluoroscopic examination to determine whether the stomach showed any abnormality, and carried out the usual detailed examination only in patients with abnormalities. Two gastric carcinomas and one lymphosarcoma were found in this manner. Both the carcinomas were early and were resected. This abbreviated type of x-ray examination used by Dr. Swenson would seem to offer the only practical means we have at present of diagnosing gastric cancer at a price within the reach of every man. Although radiologists will protest against using any but the most thorough method of examination, I would answer them by saying that it is better to have used an abbreviated inexpensive method of examination than not to have examined the patient at all. A gastric cancer picked up this way means a life saved.

For we must keep in mind that when the patient's lesion is in an operable stage his chance of cure with present day surgical technique is fairly good. The operative mortality for gastric resection has been brought down from 30 per cent to about 5 per cent during the last generation. The patient surviving resection has at least a 25 per cent chance of five year cure. Recently developed surgical techniques are making possible more and more radical gastric resections and we can hope for some further improvement in the cure rate.

CANCER OF THE PROSTATE

Carcinoma of the prostate, sixth in order of frequency, is one of the most formidable enemies of old age in men. From the viewpoint of both diagnosis and treatment our methods are very unsatisfactory, and for the moment there seems to be no immediate prospect of improving them. The radical surgical attack is applicable only to a very small group of cases where the disease is confined within the capsule of the prostate gland, and such cases are rarely diagnosed.

All of us were encouraged a few years ago by the results of orchidectomy and of estrogen treatment. We know now, however, that this therapy is only palliative. It prolongs comfort but it apparently does not prolong life.

SUMMARY

As we have traced the general course of our therapeutic attack on cancer during the last fifty years, and illustrated our theme with examples from the most frequent types of cancer, we see that very real progress has been made in the therapeutic attack. But our curative efforts have been greatly limited and restricted by our lack of good methods of early diagnosis, and our inefficiency in using the methods that we have. For the present our best immediate hope of progress in our attack on cancer is better education of physicians in the use of proved diagnostic methods. This means better undergraduate, as well as more and better post-graduate, education. About two-thirds of the physicians practicing in New York City have no connection with any hospital and they lack therefore the normal educational opportunities that hospital practice brings with it. We must help them, and it is with this purpose in mind that we inaugurate the Academy's Graduate Fortnight in Cancer.

TUMORS OF THE LUNG*

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TUMORS of the lung are of great clinical importance because of their frequency and serious significance. With few exceptions primary pulmonary tumors arise from the wall of a bronchus. Whenever the lumen of one of the larger bronchi is encroached upon by a tumor mass, the endobronchial obstruction may result in secondary pulmonary inflammation with pneumonitis, bronchiectasis and abscess formation. Most pulmonary tumors are malignant, but even small benign tumors may prove serious because of secondary infection. Pneumonitis is not infrequently the presenting feature of the clinical picture. Hence the primary underlying tumor may go unrecognized for varying periods of time.

Little can be said concerning the etiology of most pulmonary tumors. The frequency with which malignant tumors develop in an area of chronic pulmonary infection such as bronchiectasis is not sufficient to warrant the assumption of a cause and effect relationship. With respect to the increase in the incidence of carcinoma of the lung, this seems greater than can be accounted for by improved methods of diagnosis. It is possible that the present day heavy cigaret smoking may be related to the prevalence of pulmonary cancer.

Benign Endobronchial Tumors. Benign tumors which arise from the bronchial wall and project into the lumen of the bronchus are rare. Such a benign tumor, derived from one or more of the component tissues of the bronchus, may be a polyp, fibroma, lipoma, chondroma, leiomyoma, osteoma or lymphoma. Adenomas should be considered as a separate group because of their tendency to extrabronchial invasion. The benign endobronchial tumors may cause cough and wheezing but frequently the chief symptoms are due to secondary pulmonary sup-puration caused by bronchial obstruction. The diagnosis is established by bronchoscopy and biopsy unless the tumor is in a small branch

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bronchus. Endoscopic removal may result in cure if the treatment is instituted before distal suppuration has produced bronchiectasis. Otherwise lobectomy or pneumonectomy is indicated to remove the infected pulmonary tissue.

Malignant Adenoma and Cylindroma. Adenomas of the bronchus have been described under a variety of names, such as benign adenoma, malignant adenoma, mixed tumor of the bronchus, adenocarcinoma, hemangioendothelioma, etc. They constitute less than five per cent of all pulmonary neoplasms but are of considerable importance. The results which may be attained by correct diagnosis and proper treatment are excellent. Adenomas frequently show evidence of local invasion. The regional lymph nodes are occasionally involved by direct extension but only rarely without evidence of direct continuity with the main tumor. Diffuse metastasis from an adenoma of the bronchus which has not undergone obvious malignant change rarely, if ever, occurs. A very few cases with isolated metastases as chance findings at autopsy have been reported. There are a small number of cases on record in which a typical adenoma proven by biopsy was found to have years later the characteristics, both pathologically and clinically, of carcinoma of the lung with metastases. It seems best, therefore, to designate these adenomas as malignant adenomas, recognizing that usually they remain localized and grow slowly over a period of many years, but that occasionally they undergo malignant change and metastasize. The prognosis of malignant adenoma as contrasted with the epidermoid and adenocarcinoma of the lung is so different that failure to consider these two groups separately leads to an inaccurate evaluation of the results of surgical or radiation treatment of carcinoma of the lung.

The term cylindroma has been applied to a tumor which has many of the characteristics of a bronchial adenoma but which, upon microscopic examination, reveals cylinders of cells enclosing either a mucous or hyaline material. Cylindromas of the bronchus not infrequently extend up to the carina or project into the trachea. In approximately one-half of the reported cases the cylindroma either extended to the trachea secondarily or arose from the tracheal wall. Such a finding is far less common with adenomas. Cylindromas also have a greater tendency to local invasion and to metastasis than adenomas. For these reasons they are considered as a separate group of tumors, although in some instances portions of the same tumor may show both adenomatous

and cylindromatous characteristics.

Adenomas and cylindromas occur more frequently in females, in marked contrast to carcinoma of the lung. The majority of cases are encountered between the ages of 20 and 40 years but all age groups may be affected. The symptoms of adenoma and cylindroma may be caused by either the tumor itself or by the secondary suppurative process. Because these tumors are usually located in the larger bronchi, pulmonary suppuration with bronchiectasis and abscess formation occurs in the majority of cases. Empyema occurs occasionally. The symptoms due to the tumor itself are wheezing, hemoptysis and cough. Transient pain is sometimes present even in the absence of infection. When secondary suppuration develops as a result of bronchial obstruction, fever, productive cough, chest pain and other symptoms of pulmonary infection may be present. Some patients give a long history of wheezing and perhaps occasional hemoptysis. In other instances the patient considers himself perfectly well up to the time when a sudden onset of pulmonary infection, often diagnosed as pneumonia, intervenes. Failure of the pneumonic process to clear rapidly under chemotherapy, together with roentgen findings suggestive of chronic pulmonary changes with atelectasis should lead to a consideration of a possible underlying endobronchial tumor. Contrary to the statement usually made in the literature, adenomas may occur in smaller branch bronchi and in such instances may be largely asymptomatic because secondary infection is less common.

The physical findings vary greatly. Examination of the lungs is sometimes negative, but there may be localized wheezing or the physical findings of secondary suppuration and even secondary pleural involvement. Roentgen findings also vary greatly. The roentgenogram of the chest may be negative when there is a small adenoma in the main bronchus, but at this stage a respiratory shift of the mediastinum may sometimes be seen on fluoroscopy indicating partial obstruction to the ventilation of one lung. In some instances, especially if the adenoma arises from a smaller branch bronchus, a circumscribed tumor mass may be seen on the film. In many cases the roentgen findings may be those of secondary suppuration showing varying degrees of collapse of the lung and no direct evidence of the tumor itself. Planography may be of aid in demonstrating the endobronchial obstruction and may indicate the size of the extrabronchial portion of the tumor. Bronchoscopy will

usually establish the diagnosis of bronchial adenoma. The findings at this examination are often rather typical and the diagnosis can usually be confirmed by biopsy. Occasionally the adenoma arises from a branch bronchus not visible bronchoscopically. In such cases the tumor mass is seen on the roentgenogram.

Lobectomy or pneumonectomy is the treatment of choice in those cases of bronchial adenoma and cylindroma in which the patient's general condition is satisfactory. It is my policy at the present time to perform a lobectomy if the tumor can be completely removed by that procedure. Often total pneumonectomy is required because of the location of the growth. If the patient is toxic from secondary suppuration or if pleural complications are present, time should be spent in preparing the patient for radical surgery. Endoscopic removal of portions of the tumor may temporarily produce adequate bronchial drainage with diminution of the pulmonary infection. Because the tumors are vascular there is some danger of hemorrhage during endobronchial manipulation. If the patient's general condition is such as to increase considerably the risk of pulmonary resection, bronchoscopic removal of the endobronchial portion of the tumor may be of considerable benefit. In one of my cases of cylindroma there was a large extension into the trachea which responded temporarily to high voltage radiation. Approximately 90 per cent of my cases of adenoma and cylindroma are living, and all but a few are asymptomatic.

Circumscribed Benign Tumors of the Pulmonary Parenchyma. Included in this group are hamartoma, leiomyoma, lymphocytoma, neurofibroma and plasmocytoma. These tumors, with the exception of hamartomas, are very rare. They are often asymptomatic and may be a chance finding on roentgen examination. The exact diagnosis is established by pathological examination. It is rarely made clinically. Lobectomy is usually indicated. Hamartomas, often called chondromas, consist chiefly of cartilage but also contain cysts lined with bronchial epithelium. A hamartoma is very firm and may thus be confused with carcinoma at operation. Partial lobectomy is usually adequate treatment for a hamartoma.

Angiomas of the lung have been described. Hemoptysis may occur but the lesion may be asymptomatic. When the vascular spaces are large a rather free communication between the pulmonary artery and pulmonary vein may be established. Such cases have been designated

as cavernous hemangiomas or arteriovenous fistula of the lung. A large amount of blood may be shunted through the large vascular channels without the blood being oxygenated. Oxygen unsaturation of the arterial blood results. The patient may present cyanosis, clubbing of the fingers and toes, and polycythemia. A density in continuity with the pulmonary artery is seen on the roentgenogram. Angiocardiogram will confirm the diagnosis. Resection of the involved portion of the lung is indicated.

Carcinoma of the Lung. The clinical picture of carcinoma of the lung varies considerably, depending upon the topographical location of the tumor and its pathologic characteristics. In some cases a large carcinoma in the peripheral portion of the lung is a chance finding on roentgen examination at a time when the patient is asymptomatic and is at maximum weight. A small primary bronchogenic carcinoma may cause few symptoms; the metastatic lesion may be the presenting feature of the clinical picture.

When a bronchogenic carcinoma arises in the main bronchus or near one of the lobar branches, the patient may give a history of chronic cough, later productive of mucoid or blood-streaked sputum and occasional frank bleeding. Many patients, however, never have hemoptysis. There may be symptoms of secondary suppuration. A history of wheezing may often be elicited. Bronchoscopy and biopsy will usually yield a definite diagnosis in this group. When the tumor arises from a smaller branch bronchus in the mid lung field, cough and expectoration may be minimal until the tumor has attained considerable size. If no large bronchus is obstructed by the tumor mass, secondary suppuration may not develop distally, but the tumor itself may undergo central necrosis and liquifaction. When central necrosis of the tumor is marked, the lesion may be misinterpreted as a pulmonary abscess. By roentgenogram the tumor shows a thicker, more irregular wall than is usually found in an ordinary pyogenic abscess. Tumors in the mid-lung field cannot be visualized bronchoscopically, but aspiration biopsy or examination of the sputum or secretions aspirated at the time of bronchoscopy may demonstrate tumor cells.

When a bronchogenic carcinoma arises at the periphery of the lung, there may be little if any cough or expectoration, and blood spitting is usually absent. When such a tumor develops at the apex of the lung, pain in the shoulder region may be the presenting symptom, and the

patient may be erroneously treated for arthritis or other local pathology. An x-ray of the shoulder girdle may demonstrate the lesion in the apex of the lung. Sometimes this lesion is so small that it may be misinterpreted as apical pleural thickening due to old tuberculosis. These patients may have severe pain radiating into the neck and down the arm. Neurological signs, including a Horner's syndrome are present in some cases. When a peripheral carcinoma of the lung extends into the chest wall, a mass, often associated with localized pain, may be the presenting feature. An erroneous diagnosis of tumor or abscess of the chest wall may be made. A primary bronchogenic carcinoma arising in the paramediastinal portion of the lung may closely simulate a primary malignant mediastinal tumor. There may be swelling of the head, neck or upper extremities with venous engorgement, perhaps difficulty in breathing due to extrinsic tracheal or bronchial compression, and occasionally dysphagia from compression and partial invasion of the esophageal wall. Aspiration biopsy, properly performed, is of real value in the diagnosis of the peripherally located pulmonary carcinoma. Many of these lesions are obviously inoperable and exploratory thoracotomy may not be indicated. When a carcinoma of the lung is located near the lower posterior portion of the lower lobe, the symptoms may be referred to the upper abdomen, and upper abdominal pathology suspected. This is particularly true if the chest wall is involved. Occasionally a patient with carcinoma of the lung is suspected of having a primary brain tumor due to cerebral metastasis.

The early diagnosis of carcinoma of the lung is of paramount importance. As already indicated, the history is frequently not characteristic. With early lesions there may be few if any pulmonary symptoms. Hemoptysis is frequently absent. The importance of localized wheezing is not sufficiently stressed. Secondary infection may predominate in the clinical picture. Recurrent pneumonia or a pneumonia which does not respond to chemotherapy may be due to bronchial obstruction by tumor. Early diagnosis of pulmonary carcinoma depends largely on roentgen examination. The appearance of early lesions is frequently not characteristic and may readily be confused with other types of pathology. Any shadow on the roentgenogram which might be a pulmonary neoplasm calls for further investigation immediately.

The value of bronchoscopy in the diagnosis of early carcinoma of the lung has been overemphasized. The statistics from large broncho-

scopic clinics are misleading because the cases referred for endoscopy are obviously selected, and in many instances the neoplasm is seen on bronchoscopy only when the cancer is inoperable. Bronchoscopy establishes the diagnosis early only when the carcinoma arises in the main bronchus, at the orifice of the upper or middle lobe bronchus, or in the larger branches of the lower lobe bronchus. Carcinomas frequently arise more peripherally and therefore are not visible through the bronchoscope when the lesion is small. Aspiration biopsy is another method of diagnosis which deserves wider recognition. Properly performed, the risks and complications are few and the theoretical objections that have been advanced against the method are out-weighted by other considerations. Bronchoscopy, examination of the bronchial secretion or the sputum for tumor cells, and aspiration biopsy all have a place in diagnosis.

Exploratory thoracotomy is recommended in cases of suspected or proven carcinoma of the lung without evident distant metastases and provided the roentgenogram of the chest shows no conclusive evidence of mediastinal invasion. Some patients are rejected for surgery because of their general condition, advanced age and pulmonary emphysema. The most frequent cause for inoperability at the time of exploratory thoracotomy is direct extension of the tumor into the hilar structures.

Pneumonectomy is the treatment of choice in pulmonary carcinoma. Lobectomy is occasionally adequate. Resection of the lung can be performed, however, only in a small percentage of the cases because most patients have advanced disease when first seen by the surgeon. It must be realized that the favorable case of carcinoma of the lung is usually one in which the patient has few symptoms. In the last few years a considerable percentage of the cases that have been most satisfactory for resection have been chance findings on routine roentgen studies. This suggests that routine chest x-rays among the older age group, especially among males, might be a fruitful method of detecting early pulmonary neoplasms. If a lesion is discovered, valuable time should not be lost before initiating adequate therapy. Too often action is deferred in favor of a reëxamination at a later date.

Pneumonectomy is a relatively new operation. To date there have been only a few reports in which the five year arrests following resection for pulmonary cancer have been segregated from more recent cases. Consequently the summaries of some of the reports are mislead-

ing. The survival time following pneumonectomy is greatly influenced by the type of carcinoma resected. Even if malignant adenomas and cylindromas are not included, there is still a considerable variation in the malignant potentialities of different carcinomas of the lung. With few exceptions, our late good results have been observed in those patients in whom the tumor was of the slower growing type. In many clinics about 25 to 40 per cent of the patients in whom a diagnosis of carcinoma of the lung is made are subjected to exploratory thoracotomy. The percentage of the explored cases resected with a hope of cure has varied in different reports from about 25 to 45 per cent. The higher percentages are reported by individual surgeons and apply to selected material and consequently give a false impression of the actual situation in a general hospital. It is obvious, therefore, that pneumonectomy is feasible today in only a small percentage of patients with pulmonary cancer because of late diagnosis. The mortality from total pneumonectomy has decreased markedly in the past few years and is not at present a factor of major importance in large clinics. During the past four years my mortality for pneumonectomy in carcinoma of the lung has been less than five per cent.

There has been much controversy concerning the place of radiation therapy in the management of cancer of the lung. It must be realized that there are a variety of techniques in radiation therapy as there are in surgery. Radiation well localized to the tumor area lessens the unfavorable reaction from radiation pneumonitis. In some selected cases one may obtain real palliation.

Sarcoma of the Lung. Primary sarcoma of the lung is rare. Most of the pulmonary tumors reported as sarcomas several decades ago would be classified today as undifferentiated, small or oat-cell carcinoma. Clinically sarcoma of the lung simulates other pulmonary tumors, especially carcinoma. Occasionally the tumor extends into a bronchus and the diagnosis is established by bronchoscopic biopsy. Errors may occur in differentiating inflammatory tissue and sarcomatous lesions. The treatment of sarcoma of the lung is the same as indicated for carcinoma.

Lymphosarcoma and Hodgkin's Disease. Lymphosarcoma apparently primary in the lung is very rare, but the pulmonary tissue is often involved secondarily in cases of lymphosarcoma. Direct invasion from the mediastinum is frequent. Hodgkin's disease also may involve the pulmonary tissue. Extension through the wall of a bronchus is rare,

but extrinsic compression of the bronchus is not infrequent. Breakdown of the neoplastic tissue with resultant cavitation may occur. Lymphomatoid involvement of the lungs is preferably treated by radiation therapy.

Metastatic Tumors of the Lung. Pulmonary metastases are very common with a wide variety of neoplasms occurring in many primary sites. If the metastases to the lungs are obviously multiple, confusion with a primary carcinoma of the lung is uncommon because bronchogenic carcinoma rarely gives rise to multiple pulmonary metastases. A solitary metastasis in the lung, however, may be indistinguishable clinically from a primary pulmonary tumor. If a thorough clinical and roentgen investigation of other regions of the body fails to demonstrate a primary tumor elsewhere, the pulmonary tumor should be assumed to be primary and treated accordingly.

In rare instances lobectomy may be recommended for a metastatic tumor in the lung. It seems advisable to consider such therapy only if the primary lesion has apparently been eradicated and if the metastatic tumor is a slow-growing, solitary lesion appearing a long time after the primary tumor was removed.

OCCUPATIONAL AND POST-TRAUMATIC
CANCER *

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CERTAIN cancers are clearly related to industrial hazard. In the case of still others an industrial etiology has been suggested but proof is lacking and statistical evidence would never pass muster. Among the former are the papillomas and cancers of the bladder, ureter, and renal pelvis resulting from exposure to betanaphthylamine. Not only is clinical evidence clear but abundant experimental proof likewise exists. Others are the skin cancers in workers in paraffin, shale oil, arsenic, tar and pitch, anthracene, the principally scrotal cancers in mule spinners, workers in grease pits, in that vanishing occupation of chimney sweep. Still others are the actinic cancers and when one mentions actinic cancers one does not know where to draw the line of what constitutes industry. The tendency is to think of industrial cancer as mass production cancer yet this is far from a correct view point. The Texas farmer with his keratoses of the hands and face develops industrial cancer. The sailor exposed to sunlight perhaps in the Pacific area during recent years has industrial cancer of the skin and perhaps of the lip. The Egyptian farmer with the schistosomiasis of Lower Egypt, acquired in his fields, and followed so often by bladder cancer, is a victim of industrial cancer. The physician who practises the learned profession of radiology does not like it said that he exercises a trade. Is one therefore permitted to state that the roentgen cancer which he develops through carelessness is an industrial cancer? If this physician develops leukemia, is this industrial? If through roentgen exposure he acquires pernicious anemia, gastric atrophy, gastric polyp, and then gastric cancer, is this an industrial cancer? I believe it is just as were the osteogenic sarcomas in workers in the luminous dial industry during the first world war.

The fisherman who mends his nets with tarred twine which he holds between his lips may get industrial cancer. The glassblower who con-

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stantly inhales hot vapor may have industrial cancer. Certain it is that one will see cases of cancer and of leukemia in our newest group of industrialists, workers in the field of fissionable materials. The ancient Schneeberg-Joachimsthal lung cancer may be due to radioactive inhalations but the matter seems far from settled.

Statements are made to the effect that waiters and bartenders have a high incidence of esophageal cancer. Is this industrial? Do they get them because they drink to excess, are deficient, develop hepatic damage, and if so, shall we call their tumors industrial or cancers due to human weakness? And is the statement even true or does it rest on evidence as filamentous as that which assigns cancer of the nasal cavity to the nickel industry and bronchogenic cancer to the chromium industry?

Casual studies relating cancers to different industries are often casual in the extreme and would not meet the most elementary statistical analyses. In New York I am sure I could show that nasopharyngeal cancer was related to the laundry industry because we see many in Chinese and many Chinese work in laundries. Yet of course the tumor is also high in China and susceptibility to it evidently racial in Chinese. There is a high liver cancer incidence among Bantus and Bantus comprise the labor force in the Rand mines. The tumor has of course nothing to do with mining gold since the high incidence ranges over much of Africa, Malaya, and up the China coast as well.

One must not forget the fact that a cancer may be a highly individual cancer and yet an industrial cancer in the broader sense. Thus a worker will acquire a scrotal cancer if his habits are uncleanly but not if he exercises proper precautions as to cleanliness. If a man is subjected to some unusual incident in the course of industry which results in cancer it would still be an industrial cancer. Thus if a worker in hot metals receives a burn which results in extensive scar tissue formation and through years of breakdown with infection of the scarred area a cancer develops this is an industrial cancer in the broad sense. If a man working in a chemical industry develops a skin hypersensitiveness to a given agent and is treated for his lesions by an enthusiastic radiologist and after years suffers from the results of this enthusiasm one has to admit that the resultant cancer is in a remote sense industrial in origin. One does not think of any cancer hazard in the carpenters' trade, yet anyone with a very large series of cases of lip cancer may find among them the carpenter who for years has held his supply of nails between

his lips. In other words if we view industry in the broadest sense and liberalize our views as to what constitutes industrial cancer we will find not a few cases where individual behavior or individual reactions are directly or indirectly of determining significance.

Intelligent application of gradually acquired knowledge bids fair to eliminate the mass production type of industrial cancer such as betanaphthylamine cancer, but not the individual type. At present mass production cancer accounts for but a minute proportion of the total cancer of any given variety. It is probable that with the development of chemical industry we will see new chemical cancers and medicine must be on the watch for such developments. But it must refrain from hastily ascribing to industry those tumors whose incidence falls well within the expectation for the population as a whole and from making premature conclusions based on lack of appreciation of statistical methods.

Protection in industry can prevent betanaphthylamine cancer. Very large expenditure in the public health field can prevent bilharzia cancer. Industrial lung cancer is probably preventable. Bantu liver cancer may be eventually shown to be dietary and hence be preventable. Thus rather than constituting a permanent hazard in the cancer field the outlook for industrial cancer should be viewed as the most hopeful from the point of view of eventual control.

In discussing the relation between trauma and cancer one must first define trauma as we understand its implication. We mean single uncomplicated trauma. To define this further it is easier to give one or two examples of what is *not* single uncomplicated trauma. For instance, Mr. A. sustains an injury to his femur while at work. He has a compound fracture. After open reduction the healing is complicated and a discharging sinus is present which drains recurrently over a long period of years. The bone, in successive radiographs, shows evidence of an osteomyelitis which does not alter greatly over the years. Then in a relatively brief interval, more than a decade and a half after the fracture, the radiographs show a new process characterized by rather wide bone destruction. At the same time the patient develops some nodes in the corresponding groin area. These when biopsied show squamous carcinoma. The primary site is the intraosseous portion of the old sinus tract. In a broad sense we are dealing with traumatic cancer since had it not have been for the trauma there would have been no suppurating

sinus tract, but in the sense in which we understand single trauma, the case is not one in point.

Mr. B. has a bit of shrapnel in his cheek. It has been there since 1917 or '18. In 1940 or thereabouts he develops deep about the foreign body a low grade squamous cancer. It undoubtedly took origin in epidermis displaced downward by the projectile fragment. The time interval was more than 20 years during which time a foreign body had constantly been present. The trauma is a complicated one.

Mr. C. had a bullet in his hand. It is extracted under x-ray. The time of roentgen exposure used in extraction is said to have been, incredibly enough, 45 minutes. Mr. C. hasn't got cancer yet but most certainly will, but it will be roentgen cancer and not cancer due to the bullet.

A thorough discussion of the relation of cancer to single trauma would require many hours and is obviously impossible in the time allotted. I prefer therefore to discuss single trauma as it pertains to a few varieties of malignant tumors which tend to reach our compensation courts with a fair degree of frequency. Whereas it must be freely admitted that cancers differ in immediate etiology and that argument directed toward the elucidation of one form may by no means apply to another, nevertheless in presenting a thesis in defense of a point of view applying to one specific type, one can develop patterns of reasoning applicable to others. Let us first consider bone sarcoma. I choose bone sarcoma because it is a tumor where many so-called "authorities" would admit traumatic etiology. What do we know about the etiology of bone sarcoma? A certain number arise in long standing osteochondromas, usually central. Another group arises in Paget's disease. A small number have been found in patients suffering from the effects of ingestion of radioactive materials. This etiology has been confirmed also experimentally. A recent report describes multiple origins of osteogenic sarcoma in experimental beryllium poisoning. Another after radioactive strontium and plutonium. Some few have occurred as the consequence of radiation of benign lesions of bone or of "benign" giant cell tumors. I have seen osteogenic sarcoma as the sequence of radiation of retinocytoma in infancy. I have seen two examples of osteogenic sarcoma, one case multiple, arising in Gaucher's disease of bone and several in fibrous dysplasia. This leaves a large number of primary malignant bone tumors unaccounted for and at present we have no explanation of their existence. This fact however does not mean that we must look for

such explanation in trauma.

The sincere investigator works under great disadvantage when he endeavors to elucidate the role of trauma. Hospital histories usually taken by residents are of essentially no value. Statements of patients are accepted as bona fide and go down in histories without critical analysis and without the slightest evidence of skepticism. When a case reaches a compensation court the claimant's testimony is of no scientific value whatever despite what a referee may think. The stories told may combine the best features of Baron Munchausen and Alice in Wonderland.

Unfortunately I do not believe that medical testimony of the average sort is much better. First of all the physician unfortunately is testifying for a fee or in order to collect a bill for services rendered and I am sufficiently skeptical of my colleagues to believe that some, at least, share the common herd's instinct to collect where they can. I feel therefore that any case of medicolegal import is *prima facie* one where an attempt at scientific evaluation is apt to yield material of very doubtful significance. This at once restricts material to be analyzed to cases with no medicolegal import. Now it would seem that they might afford an answer but they do not. They do not because the average surgeon does not know how to question a patient. If I had my way I would turn over every such case claiming trauma to a psychiatrist to see how an original story of trauma would end up. I have reason to believe that the end story might be far different from the original.

We might ask ourselves what accessory evidence can be brought to bear concerning traumatic etiology of bone sarcoma. I believe the accessory evidence of negative character greatly outweighs the supposedly direct evidence of positive character. Thus: the supposedly precipitating trauma is usually mild or even minimal. In a previous lecture on this subject I have called attention to the fact that I personally had seen no osteogenic sarcoma following the maximum trauma of fracture. Since then I have seen one possible one although I regard the prior integrity of the bone as doubtful. Statistics are hazardous things. I am however informed that perhaps once in ten years in New York State an osteogenic sarcoma within a year of fracture might occur in a given bone on the basis of chance alone without etiologic relationship. It so happens that I see a large number of the osteogenics originating in this State—what exact proportion I cannot say—and that I have had one such case in 18 years. I make no claim for the validity of the statistics and as

stated above am by no means sure of the primary integrity of the part in the instance concerned. Be that as it may it is still a fact that the severest trauma to bone, namely fracture, is the least apt to yield sarcoma. Further accessory evidence of negative character comes from surgery. Surgery involves screws and ice tongs, removal of wedges for correction of deformities, resections with insertion of grafts, highly traumatizing spine fusions, and yet no sarcomas seem to result. The highly disruptive lesions of Charcot joint or syringomyelia produce no cancers. The multiple infarcts of caisson disease seem to "heal" without event. If subperiosteal hemorrhage causes regenerative changes leading to sarcoma why do we not hear of it from the hemorrhages of scurvy? The prolonged inflammatory changes in bone resulting from osteomyelitis do not result in tumors. When sinus tracts lead down to bone and one has excavations with prolonged suppuration the cancer which develops is always squamous carcinoma and never osteogenic sarcoma. One of the most traumatizing procedures to bone is found in one of the commonest operative procedures on man, namely exodontia, and whereas osteogenic sarcoma leads to exodontia under mistaken diagnosis, the reverse never seems true. The proliferative periosteal changes which accompany other tumors, of which the most striking example is meningioma, although they may exist over a period of many years do not result in the conversion of the process to osteogenic sarcoma. Thousands of amputations have been performed since the early days of surgery and although one saws through bone, regularly elevates periosteum, possibly uses forceps or rongeurs to improve the appearance of the stump, we do not see any rapidly developing fungating sarcomas as sequelae.

How common are malignant bone tumors unsuspected by the patient? We naturally cannot say. I have seen them. I had a couple of years ago an unsuspected malignant bone tumor of a rib discovered in a draft board examination. Dr. Jaffe informed me a few months ago that he had found a very early osteogenic sarcoma in a patient who had a film taken immediately after a bona fide trauma. Had that film not been taken the case would have in all probability fulfilled the criteria for traumatic osteogenic sarcoma. It is certain that a number of chondromas are encountered as incidents of radiographic study for other conditions, and that chondromas constitute foci for later development of sarcomas.

One derives the impression that malignant bone tumors have rather highly specific causes which so far remain unelucidated. Specificity for

example appears in the high incidence of osteogenic sarcoma in Paget's disease and the essentially zero incidence in generalized osteitis fibrosa cystica. It may also appear in the case of the solitary central chondroma as a source of sarcoma on the one hand, and the lack of evidence on the other of sarcomatous tendency in the case of the epiphyseal chondroblastic tumor described by Codman. Proponents of the theory that post-traumatic regeneration of bone is of causal significance in development of sarcoma should be exposed to the histologic appearance of normal bone growth at epiphyseal lines where absorption and growth are coincident phenomena over the entire life period of bone growth. True it is that these zones are likewise the common site for osteogenic sarcoma but if post-traumatic regeneration causes the majority of bone sarcomas then I cannot see why most people with normal bone growth don't develop this disease since all of us exhibit essentially the same regenerative phenomena without any trauma.

In emphasizing normal processes in tissues or organs which duplicate exactly effects ascribable to trauma I like to use one very pertinent example. This is the uterus. One does not hear of uterine cancer being ascribed to trauma yet there is in existence plenty of testimony to the effect that cancer of other mucosal-lined viscera may be so ascribed. The facts are, of course, that the uterus of the normal female traumatizes itself physiologically every 28 days from about the age of 14 to 15 in these climes to that of 45 to 50 or upward. The average female sustains some 400 traumas all accompanied by hemorrhage, slough, and very active regeneration. The average female who gets a carcinoma of the endometrium does so some years after all trauma has ceased. Similarly the ovary traumatizes itself once a month yet no one considers an ovarian carcinoma traumatic.

The normal wear and tear of life induces a multiplicity of traumas which are rarely noted or quickly forgotten until the time arises to make something out of them. I strongly advise the advocates of the traumatic etiology of cancer to take a few hours off from their deliberations and concentrate upon observing a group of children at play. They will. I can assure them, in the course of an afternoon witness all the types of injury supposed to cause cancer and unless hard-hearted will return home greatly depressed at the sad outlook for the future these children possess.

Advocates of the role of trauma rarely if ever consider a role for in-

fection in the genesis of cancer. I would think that if trauma possesses a role, then infection should possess an even greater one, for the tissue changes of infection would seem to resemble although in more severe form those of trauma. In infection tissues die, exudates accumulate, vascularizations occur, scar tissue results, and parenchymatous tissues are stimulated into regenerative growth. Yet the individual who testifies that a bone sarcoma has arisen because of trauma would not worry about a case of osteomyelitis eventuating into osteogenic sarcoma. He does not think that a breast abscess will become a breast cancer, a lobar pneumonia a bronchogenic cancer, an amebic abscess of the liver a hepatoma, a carbuncle a liposarcoma, a psoas abscess a myosarcoma. He has never professed an opinion that the proliferated nuclei in widely disseminated foci in that very common disease trichiniasis form the starting point of muscle sarcoma. For the most part these things have never entered his head because he has promptly forgotten his pathology after the end of his sophomore year in medical school.

But be that as it may, we have gotten away from bone tumors. Some years ago I formulated a brief statement in the course of talks to medical students. Facetiously I called it Stewart's Law and it goes like this: The probability that a given lesion is a primary bone sarcoma, all facts being correctly stated, is inversely proportional to the degree of trauma sustained. This statement has been improved by my associate, Dr. Foote and might read "To establish the traumatic origin of tumors requires that one be able to prove that trifling injuries are vastly more cancerigenic than are major injuries."

Mammary cancer appears with fair frequency in our compensation courts. It is a common disease and the minds of many women have been through generations impressed with the fallacy that breast cancer follows a blow. Surgeons and to a lesser extent pathologists are misled by careless statements in books and fail to reason on the basis of facts which of course they may not even know. Now mammary cancer in the human subject is largely a disease of mammary ducts. It has been said that traumatic mammary cancer may follow the "rupture" of ducts but the trouble is that no one sees "rupture" of ducts until the cancer is already lining these ducts. The commonest cause of severance of mammary ducts is surgery performed for benign lesions of the breast. If this is the commonest cause of breast trauma then it should be the commonest factor in etiology of cancer. Some support might be supposedly derived

from statements to the effect that patients operated on for benign lesions—notably the various manifestations of cystic mastopathia—have a higher than expected incidence of subsequent mammary cancer. This is true *but* the difficulty is that the higher incidence may be in *either* breast, the operated one or the intact one. This of course negatives the influence of trauma in the causation of breast cancer and throws the emphasis to the field of cystic-proliferative lesions of the breast whose influence is in turn most difficult to ascertain through actual statistical study although few with large experience could question its participation. Most surgeons fail to appreciate the fact that when they see a mammary cancer which they can feel it has been there a long time and has been preceded by a progressive transformation of a region or regions of the duct system leading to the development of a carcinoma in situ. It is impossible to say just how long this phase lasts but if we judge from evidences presented in those fields where chronology is somewhat known we might extend the in situ period for several years, perhaps five and maybe more. Furthermore, cancer of the breast is a system disease, often bilateral, and successive segments of the mammary apparatus are involved first by an in situ and later by an infiltrative type of lesion as the attribute of malignancy in the cancer cell becomes more and more manifested. The acme of change is reached in the extensive bilateral type of disease. I would refuse to entertain even the suspicion that mammary cancer is caused by trauma. One of the most convincing cases for traumatic etiology is that reported by Rixford and seen and partially accepted by Ewing. We might ask how the evidence stacks up. The patient was a boy of about 17. He struck the right breast and sustained a verified trauma. The breast swelled to large size. Treated conservatively the swelling diminished and 6 months later a rather small flat discoid lesion persisted below the nipple. A surgeon locally excised it and threw the tissue away stating that it was like other gynecomastias which he had seen. No tumor subsequently appeared in this breast and in fact the next *external* evidence of disease was found in the *opposite* axilla. The patient later died with widely disseminated lymphatic permeation and metastases in the neck, both axillae, mediastinum, mesentery, about the prostate, in the skin of the trunk, and in fact “everywhere except in the skin and subcutaneous tissues of the right breast, the site of the surgical operation.” Parenchymatous metastases were rather rare. No primary tumor was found at autopsy. I have seen these sections and to

me the lesion looks more like a gastrointestinal than like a breast cancer since the cells possess mucus droplets and a trace of signet ring structure. Growth too is more papillary than is to be expected in disseminated breast cancer. Neither the age of the patient, the sex, nor the distribution of disease fits the story of breast cancer. The fact that no primary was found does not impress me because I have myself failed to find primary tumors occasionally and recall one case seen by the late F. B. Mallory where an insignificant primary was nearly missed and was in fact only discovered after the body had been reopened and a tiny lesion of the ampulla of Vater detected. All sorts of traumatic incidents are described by claimants seeking compensation for breast cancer. They range from the sublime to the ridiculous. I recall one case where a lady fell on her back and pressed a small drinking cup to her capacious bosom and this incident had to go through the usual routine of the compensation board. I recall another, not of medicolegal import, where a lady had attended the funeral ceremonies of a friend who had unfortunately died of breast cancer. She was greatly worried and immediately examined her own breasts and found a lump which proved to be cancer. Perhaps that is a case of acute psychic trauma. One can almost see the frenzied activities of the neural mechanism on the way back from the cemetery, the acme of psychosomatic medicine.

The earlier one sees mammary cancer the less one is apt to see any suggestion that an episode has occurred in the surrounding tissues which could have been produced by trauma. One does not see evidence of old hemorrhage. One does not see undue fibrosis save in the breasts which are already extensively fibrosed and atrophied. One does not see the cancer within the ducts accompanied by inflammation except as a *result* of the cancer and in fact the striking pattern in the earliest phase of breast cancer within ducts or their terminal lobules is the utter lack of anything abnormal whatever besides the cancer except in some instances its predecessor, the papillary hyperplasias. Everywhere one gets the impression that the cancer process is something intrinsic within the cell of origin uninfluenced by external or for that matter internal factors which show themselves through perceptible alterations in surrounding tissues. Here and there a few cells are cancerized and if one wished to invoke trauma in explanation the trauma would almost have to be induced by use of something like a Chambers micromanipulator.

Whereas a survey of older textbooks particularly of surgery pro-

duces numerous statements to the effect that breast cancer may be traumatic they belong for the most part to the category of books which state that breast cancer *follows* eczema of the nipple and the two statements are of equal validity, showing equal pathologic knowledge. Late publications issued by anti-cancer organizations such as that in Massachusetts tend to deny these obsolete theories. One only, issued in Minnesota, is unwilling to deny the traumatic etiology. I suggest that this represents someone's personal idea since *only breast cancer* is mentioned as possibly traumatic, and no others. It is strange that it would assume this unique position.

A third group of tumors commonly ascribed to trauma are tumors of the testis. The fact that an identical type of tumor, which without statement as to location could not be distinguished microscopically from these testis tumors, happens to occur in the ovary where surgeons do not incriminate trauma, attracts little comment. Strangely enough, too, they occur in the pineal gland. In the ovary they are known in the pre-ovulatory age group and hence "normal" traumatic incidents cannot be invoked in explanation. Likewise the fact that testis tumors occur in abdominal testes where the organ is far removed from trauma is strong evidence against the traumatic hypothesis. There is considerable evidence to incriminate developmental disturbance of unknown origin as a factor in production of testis tumors. Thus although pseudohermaphroditism is not a common state it accounts for about 1 per cent of testis tumors and in these cases as reviewed by Gilbert who analyzed some sixty, forty-eight were in abdominal testes, eight in inguinal testes and but two in a scrotal testis. Eight were bilateral.

Concomitant ectopy occurs in 11 per cent of testis tumors, or forty-eight times the chance association and in unilateral ectopy the tumor is in the ectopic organ in 97.5 per cent of all cases. When a testis tumor occurs in a "normal" testis the chance of its being bilateral is but 1 per cent but when bilateral ectopy is present the chance of bilaterality of tumor rises to 11 per cent. Wells reports seminoma associated with complete failure in development of the right genital anlage and immaturity of the left anlage. On the other hand there is no suggestion that the incidence of malignant testis tumors is increased by the trauma concerned in orchidopexy and the interval between surgery and tumor ranges from 5 to 12 years in teratoid and unicellular types respectively.

A testis may be the site of unsuspected tumor. This has repeatedly

been shown in instances where the first suggestion of disease appeared from distant metastases and the primary tumor was only demonstrated by careful autopsy study. I have seen testis tumor in supposedly non-neoplastic ectopic organs removed at herniorrhaphy and one in a testis removed immediately after a severe scrotal trauma where crushing of the testis was present. The latter would have constituted a perfect case for trauma had the testis not been removed in a matter of hours.

That tumors occur in supposedly normal testes has received confirmation from veterinary studies. A fairly recent report disclosed three unsuspected testicular tumors of horses in the course of 250 gelding operations. The various inflammatory lesions affecting the testis, although so far as tissue changes are concerned these lesions should count as a histologic equivalent of trauma, do not seem to influence the incidence of tumor. Thus in 5500 testis tumor records Gilbert found records of orchitis due to mumps in but twenty-four and an average interval between orchitis and tumor of 12 years—just about the difference between the average age incidence of the two diseases.

I have heard the statement made that in 30 per cent of testis tumors the disease is due to trauma. One immediately asks what causes the other 70 per cent. To make such a statement is to my mind the equivalent of saying that 70 per cent of cases of smallpox are caused by a filtrable virus but the other 30 per cent are caused by trauma. The fallacious approach is very obvious and were one to think back over decades and centuries there is scarcely a disease to which this form of false logic could not be applied, for in the infancy of medicine etiologies were wholly obscure and had there not been available a host of malign influences and a vast source of magic, undoubtedly trauma would have played a much greater role than it ever did, in the field of disease in general. In my own early days I learned on local medical authority that a certain child in the neighborhood had acquired paralysis, clearly poliomyelitis, because the nurse had dropped him. Why an identical twin had gotten it within hours thereafter was not explained.

As one author succinctly expresses himself "Because toads appear after a rain it is not necessary to assume that it has rained toads," yet this form of reasoning fills our medical testimony concerning trauma.

Advocates of the traumatic etiology of cancer, aware of the difficulties which underlie their suppositions, may take some refuge in the thesis that the individual who suffers from what they term a

traumatic cancer is one who possesses what they call a predisposition. They do not define predisposition but I understand the term in two different senses. First it might mean a hereditary reaction pattern to the injury sustained and I would widen their use of this definition to state that without hereditary reaction pattern in its broad sense no tumor can occur and that the function of biology is to determine these reaction patterns and the factors of realization which bring them into evidence. Secondly they may mean that a set of conditions, perhaps the existence of something in the nature of a virus or chemical agent, may already obtain in the injured area which agent may give rise to tumor when the soil is suitably traumatized. Some take refuge in the essentially obsolete Cohnheim theory of surplus cells which are thought of as only awaiting a suitable trauma to goad them into action. Unfortunately no one has seen these cells. What is curious about the thesis of predisposition as commonly maintained is that its proponents neglect the temporal factor. Evidently it is only at one time when the malign influence of trauma can give rise to cancer. The part injured may have been injured almost ad lib at other times and nothing unusual happens, or it may be that injuries to other constituents of a system, muscles, bones, or soft tissues occur at the same time but only in the temporarily predisposed part does tumor arise. The great difficulty is that human medicine has no method of answer to such suppositions and hence cannot deny them and unfortunately they are not subject to experimental proof or to complete rejection on logical grounds. One cannot argue without fact.

I have emphasized the unreliability of hospital charts relating to injury. I could give illustration after illustration to support this conclusion. Statements by patients may be deliberate falsification but are often unconscious misstatements. I could cite you the case of a man with a bulky basal cell tumor of the skin of the temple which was related to a blow from an iron bar through many medicolegal squabbles but which was admitted to have long antedated that alleged injury after the claimant had become slightly enamoured of a social worker to whom he confessed. Within the last few months I had an accidental example of the inadequacies of history taking in the shape of a story told by an employee of my own apartment. The story did not involve compensation. The patient had an extremely advanced tongue cancer which he related to injury from a fish bone. That he had stuck himself with the bone was beyond shadow of doubt because he was so impressed by the injury

that he kept the bone wrapped in a bit of paper in order to exhibit it to on-lookers. Still he had stuck himself twice with the same bone and the tumor was well back in the tongue which made me suspect that an organ twice severely traumatized could scarcely have been of normal motility or sensitivity. I questioned the man myself and he denied any evidence of prior disease until I was about to give up the inquiry whereupon he added as an innocent afterthought the statement that there was "nothing except that when I smoked a cigarette it burned me back there. When I stuck myself it bled and bled and bled." One does not forget that in giving the findings when a small biopsy is secured from an open lesion one of the commonest statements one sees on a history sheet is "lesion bleeds easily."

I will never forget a curious example of the casual in history taking in a case in the Memorial Hospital where the chart states that the patient had been bitten by a duck. This statement persisted for years and excited no curiosity until viewed by a resident who knew something about ducks. He asked the patient what sort of duck had bitten him whereupon the patient responded "It vos a bool duk."

About two years ago a certain letter appeared in the Journal of the American Medical Association. It was apparently written in rebuttal of one written by me in which I called attention to the credulity of physicians and courts in the acceptance of the doctrine of single injury as a cause of cancer. The writer obviously considered that his rebuttal was just and complete. He dealt with facts as he had them, or rather *hadn't* them, and I hope to use this particular proceeding in order to show what cannot be accepted in evidence. First I quote portions of the published letter: "In April 1935 about 11 P. M. in S——, Kansas, P——, in the course of his employment, was carrying a box of books. He stumbled, the box struck and damaged the top of a desk and P's chest struck the box. Before quitting work about 1 A. M. P—— left a note for his supervisor reporting the accident. Whether or not he reported that he had been hurt is unclear but when he reached home he told his wife of the accident, and that his chest had struck the box and was hurting. There was no evidence up to that time that he had suffered any chest pain. His wife did not examine the chest until 3 or 4 weeks later. Then she found a red spot. A month to 6 weeks, possibly 2 months after the accident he told his supervisor that he had hurt his chest when he fell with the box of books and that the lump on his chest was caused

by the bump or bruise." Then the writer of the letter asks the following evidently rhetorical question: "Was not the injury described the exciting cause of the sarcoma that followed. Before denying a causative relation one should point out some reasonably likely cause other than the injury. Before attributing the entire incident to the so-called laws of chance one should consider the incidence rates of sarcomas of the sternum and of contusions of the sternum on the entire population and then estimate the chances of such contusion and such a sarcoma coincidentally in site and in immediate chronological sequence."

Now to me this sounded like a striking case and evidently the courts thought so too for they awarded full compensation. But it sounded too good and I wrote for copies of the testimony and reviewed the situation at length. After this review I can honestly say I have never seen a more extraordinary situation. Let us briefly review the facts apparent in testimony. The claimant was the patient's wife, the patient having died. Hence most evidence was hearsay. The patient was a janitor. He did mar a desk. He reported this by leaving a note for his superior. The latter destroyed the note. He testified that he recalled the note stating that damage had occurred to a desk but recalled nothing about the patient stating that he had hurt himself. But the commissioner ordered stricken out the last part of this testimony about the patient not having stated that he injured himself thus concealing what to an unprejudiced person is important. Still perhaps that is correct procedure for later on the fact is brought out by direct questioning. Then it appears that the wife's testimony is accepted as bona fide. She testifies that when the patient came home "he said that his chest was hurting him awful bad." She does not state that the husband told her he had reported an injury to his chest but believed so. Despite the fact that the patient's chest was hurting him very badly this loving partner did not see fit to examine the allegedly injured part and only did so some weeks afterward. Incidentally even the date of this injury appears uncertain. It might have been in February, March or early April. It would seem to me that a bona fide injury might have been more definitely placed in time.

Now later on it appears that the patient was told by the doctor that his lump was due to an injury. The alleged relationship was something stimulated by a physician looking for a cause for something he didn't understand. One wonders if the patient were not more astute than the doctor because the former never filed any claim for compensation during

his lifetime and the institution of claim seems to parallel roughly the receipt of bills for medical and funeral expenses.

Nowhere in the testimony does it appear that first appearance of tumor and site of alleged injury corresponded. To cap the climax there is not a shadow of evidence that the man had a sarcoma at all for the material removed at surgery was thrown into the bucket without pathological examination.

Have we any right to assume that the fact that the operator made a diagnosis of sarcoma proves it to have been? I could not myself from gross examination alone and the very fact that this patient was seen by physicians for a period of 13 months prior to operative interference does not convince me that diagnostic acumen in S——, Kansas is on a higher level than that in New York. Then I am interested in the radiographic findings. The tumor was destructive, destroying sternum and rib cartilages. This sounds to me like a metastatic carcinoma and from my past experience with sternal tumors I would hazard a substantial bet that Mr. P—— had either a penetrating lung carcinoma or a metastatic renal cancer. It is interesting to note that his physician had for some time prior to the alleged accident been treating him for "bronchial trouble."

I believe the rhetorical question posed in the Journal of the American Medical Association is fully answered. I cite this case as an almost perfect example of the hopeless character of analyses we find in many cases where questions of traumatic etiology of cancers are raised.

It must be quite obvious that none of the postulates, in which the medicolegal expert has for years taken refuge in acceptance or non-acceptance of a given case as traumatic, are fulfilled in the latter case. I do not propose to discuss these postulates save to say that they are only exceedingly rarely fulfilled in any case of traumatic cancer so-called. In fact it is in many instances frankly impossible that they can be fulfilled. I do however wish to call attention to the fact that, when in the rare case they are, it really means nothing at all and the reasoning involved in acceptance of a traumatic etiology of a cancer is still of post hoc ergo propter hoc type and as science it has no value whatever. We still do not know what causes the tumor and our reactions are conditioned upon emotional rather than scientific grounds. Let us not forget however that we do have a very ready source of material for study where all the necessary postulates demanded by the medicolegal expert

are at hand, prior integrity of the part, exact extent of injury, specific tissues injured, exact site traumatized, known time factors and everything. That source we have mentioned in passing but should now emphasize in concluding and the source I refer to is surgery. More tissue damage is done by surgery than by any other form of injury and I have yet to meet the surgeon who can recall the fact that his years of activity have produced a single tumor, other of course than a simple keloid which never becomes malignant, or an amputation neuroma, likewise benign. It is doubtful if either of these lesions should be dignified with the name of neoplasia.

I have said nothing about the role of trauma in accentuation. To discuss this would require considerable time. Accentuation has to be evaluated on the basis of knowledge of natural history of the disease in question. It is not enough to accept accentuation as a fact in the case of an individual who has sustained a trauma to a tumor and has thereafter experienced what may be supposed to be unusual growth activity on the part of the tumor. The change in behavior must be something *praeter naturam*, beyond "nature." As one's experience in the spontaneous behavior of neoplastic diseases increases the fewer will be these unnatural alterations in behavior until they almost approach a vanishing point. Let me cite two examples to illustrate our difficulty: Mr. A. has a tumor of the upper end of the humerus. The periosteum is elevated but intact and growth is proceeding under the restraint of a tense capsule. A surgeon cuts down on the lesion, enters the periosteum, secures a specimen, does not close periosteum or the tissues in layers but instead leaves in a drain. The tumor rapidly fungates. This is accentuation. The tumor may in a matter of two or three weeks become inoperable. On the other hand Mr. B. has had a rib tumor for 5 months at least. On July 5th this rib and the two adjacent ones are resected down to and including parietal pleura. The chest is open and careful inspection reveals one tiny pinhead size nodule on the diaphragmatic pleura. This is tumor. Nothing else is seen. A nodule is felt in the underlying lung which is decorticated. This nodule is a Ghon tubercle. The convalescence is uneventful. The tumor itself has not been touched. The patient is discharged on the 11th day feeling well. About three weeks thereafter he suddenly feels weak, becomes dyspneic, and has a temperature. He re-enters the hospital where it is thought that he has a late postoperative effusion. He is tapped and only blood is obtained. He

dies less than two weeks later and at autopsy the pleura, previously clear, is overgrown on all its aspects, from base to apex and from parietal to mediastinal, with a sheet of tumor two inches thick and both lungs, clear five weeks previously, are riddled with tremendous metastases. I stated that the first example represented traumatic accentuation. After the second where tumor was not touched, we must ask ourselves, does it?

In conclusion were I required to state my position on the relation of single trauma to cause of cancer I would state it briefly as follows:

Attempts to rely on single trauma to explain cancer depend on the exercise of primitive forms of reasoning.

They represent a carry-over from pre-pathologic days and appear in textbooks which copy from one another and are repeated by writers who do not think or who lack the wherewithal to form judgment.

They are propagated by a system of compensation medicine which denies payment for services to a physician who may in good faith have assumed care of a patient, unless that physician shall prove a traumatic etiology for the disease, and since the physician is human and can find plenty of so-called authorities to support such etiology he is very apt to endeavor to prove it, although I would warrant that for the most part he does not believe it himself.

They are likewise propagated by patients who lack information on origins and natures of disease and who for years may have been conditioned to relate lumps and therefore cancers to blows. Such patients readily fall into faulty logic especially with lay, medical, and, above all, legal aid.

They constitute a small but steadily increasing problem in sociology which I do not pretend to be able to solve.

SKIN TUMORS *

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DISASTROUS results from cancer of the skin are in almost all cases avoidable by removing the irritants known to influence the development of cancers, and by thorough treatment of pre-cancerous and cancerous lesions.

Skin cancers in their incipiency and throughout their entire course are interesting in that they are an open book, so to speak, that he who will—and can—may read.

As you know, there are three main types of skin cancers: The basal cell epithelioma (benign, non-metastasizing); the squamous cell epithelioma (metastasizing); the malignant mole or melano-carcinoma.

Basal cell variety: There are a number of different types, the most important being the rodent ulcer, the morphea type and the multiple benign superficial basal cell epithelioma. The particular variety of basal cell epithelioma probably depends upon its location, the carcinogenic factor and the tissue from which it originates. Rarely are there symptoms connected with the two latter varieties of superficial growths, except that occasionally one may ulcerate, simulating Bowen's disease (dyskeratosis). While each of the basal cell types may differ from the others in appearance and in the degree of local destruction, all have certain features in common, the outstanding one being the pearly or waxy telangiectatic margin or rim. They are slow growing, cause only local destruction and probably never metastasize. Metastasis is so rare that when it is observed, one must question the correctness of the diagnosis on the original tumor.

The rodent variety is usually the most destructive of the group, and over several years' period may cover a wide area and cause considerable destruction, especially where an irreplaceable part is involved, such as the eyelids or nose. Such ulcerations sometimes have to be differentiated from the gumma of syphilis, tuberculosis and blastomycosis, though usually the history of several years' duration, the waxy or pearly nodu-

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lar border, the crusted and red, bleeding granular base, serve to identify the epithelioma. The duration of lupus is usually longer than epithelioma. Biopsy should make the diagnosis conclusive.

I have seen recently three cases of gumma which had been diagnosed and treated by radiation for carcinoma, the treatment being followed by a severe reaction, including redness, swelling and sloughing of the parts. Gummas are apt to be found on an extensor surface at the site of trauma. They develop rapidly, usually are kidney-shaped, with deep, punched-out bases and bevelled, soft edges. The Wassermann is almost always positive.

Tubercular ulcers usually are distinguishable from carcinoma by their ragged, undermined verrucous edges, and by the tendency to heal with scar formation and, oftentimes, with recurrence of tubercular lesions within the scarred area.

Blastomycosis is a warty, crusted lesion with multiple discharging sinuses. The fungus can most often be demonstrated.

The morphea variety, as the name implies, often strikingly resembles scleroderma. The lesions may vary from pea-size to that of a man's hand and be shiny, smooth, the color of yellow wax, and have a slightly raised telangiectatic margin. These lesions never ulcerate and, except for appearance, cause little or no inconvenience.

The multiple superficial basal cell epithelioma, contrary to most of the benign types, which usually appear on exposed parts (chiefly the face) is found on the covered areas, often the trunk, arms and thighs. These lesions vary in number from one to a hundred or more, and in size from a small pea to—in exceptional cases—that of one's hand. They are deep red, scaly, with scarring in the center and with a threadlike characteristic pearly border. These growths are sometimes mistaken for and treated as psoriasis—as was a case which came under my observation a few weeks ago. This patient was suffering from an active pulmonary tuberculosis, and inasmuch as there had been no response after a year's treatment for psoriasis, the physician who had sent him to me thought that the skin lesion might be tubercular.

Most of the patients with the superficial basal cell epitheliomas have been under treatment with arsenic in earlier years, and it is now believed by many physicians that this drug may be responsible for the growths. Indeed, in many instances, arsenic in excess may be demonstrated in the blood and urine of such patients.

Squamous cell carcinoma (the metastasizing variety), while relatively benign and usually accessible to removal may, if neglected, or mistreated, spread to the internal organs and cause death. These growths may occur on any part of the cutaneous surface, but they are more often found on the extremities and uncovered parts, and at the site of some long-standing irritations, such as x-ray burns, scars, chronic ulcerating skin diseases, in arsenical keratoses, in cutaneous horns, in xeroderma pigmentosa. All tumors beginning on mucous membranes are of the squamous cell variety.

Characteristics of this sort of tumor are: its comparatively rapid growth, an accompanying inflammation in and around the lesion, the verrucous ulcerating and sloughing base, and the hard nodular borders. Some early and atypical lesions cannot be distinguished from basal cell epithelioma without a biopsy. While it is generally thought that most carcinomas that form in an x-ray burn are of the squamous cell variety, it interested me to find that under biopsy study of the last eleven such growths I have removed, eight proved to be basal cell epithelioma, two squamous and one baso-squamous.

I believe it imperative that one take a biopsy, either before or at the time of treatment of every epithelioma; not only is such laboratory information of diagnostic value, but often one can determine the depth and the degree of malignancy. It would seem that whether a given skin tumor proved to be of the basal cell or squamous variety, might depend on the location, the duration and the degree of irritation.

Melano-carcinomas, the third group, are by far the most malignant of all skin tumors, though the degree of malignancy may vary considerably in different individuals, according to the age of the patient, the location of the primary lesion and the type of tissue from which it originates. For example, a melanotic nodule appearing on the cutaneous surface of an adult may cause metastasis and death in a few months, while a similar growth on a child may require many years to cause death.

I have in mind three cases in which melanotic growths were removed from the eyes of children—and in one of the cases, a few months later a similar melanoma from the forehead. The diagnosis was in each case confirmed by a pathological report, yet these patients after 20-26 years are still well. The prognosis in cases of melano-carcinoma arising in the skin is also much more favorable in children.

Melanoma is first noticed as a pinhead to a pea-sized, bluish or brownish-black papule, more often on the sole of the foot, around a toe or finger nail, on the buttocks or on the forearm. The lesion increases gradually so that in six months or a year it may be the size of a hazelnut, with bluish lines radiating from the tumor. At this time the regional glands may or may not be enlarged. Then pea or almond-sized nodules may appear beneath the skin near the original lesion and spread gradually over all the cutaneous surface; the glands, liver and the spleen become enlarged. Melanine is found in the urine. Sometimes these melanotic growths originate from moles which have been subjected to frequent irritation or that have been incompletely removed. Such tumors are highly malignant and usually terminate fatally.

Melanoma must be distinguished often from blue nevi, fibro-angioma, epidermal nevi, pigmented basal cell epithelioma and from pigmented moles. Blue nevi have usually been present and unchanged since childhood, or for many years, and are dark blue to black in color and sharply circumscribed. Rarely does one become malignant, and if it does, it is usually a melano-sarcoma.

Fibro-angiomas are most often on the face, and are hard, lobulated, blue in color, and have usually been present for a year or more without noticeable change. Epidermal nevi may be from pinhead to pea-sized, macular, tan to dark brown in color. The pigmented basal cell epithelioma may be recognized by the history of a keratosis of several years' duration, and the verrucous, ulcerated character of the lesion, and the pearly border.

Any pigmented moles of a dark color which have been irritated always arouse the physician's and the patient's fear of melanoma, but these can usually be readily differentiated from such by the absence of any change in surface markings and the absence of a smooth, nodular growth in or at the margin of the mole. Hairy moles very rarely become carcinomatous.

The pathological diagnosis of tissue suspected to be melanotic is sometimes just as difficult to make as is an exact clinical diagnosis. I have, on more than one occasion, known several of our most able pathologists to differ as to whether the sections showed benign or malignant pigmented growth.

For example, not long ago, I was asked to see a boy of 11 with a bathing-suit type of deeply brown pigmented hairy nevus covering

most of his trunk. A biopsy had been taken of the nevus when he was an infant and again two years later, and both specimens were reported by the pathological department of a well-known medical school as melano-carcinoma. In the meantime, the boy had developed normally and was strong and healthy in every way. Specimens of the growth were submitted to the pathological department of a local medical school, where the diagnosis of melano-carcinoma was confirmed. When the boy was presented to the New York Dermatological Society, the consensus was that the boy had only a bathing-suit type of hairy nevus.

From instances like this it becomes apparent that we must correlate our clinical findings with those of the laboratory in order to arrive at a correct conclusion.

Prevention of Epitheliomas: In order to safeguard against the formation of these cancerous skin lesions, we must recognize the condition under which such growths develop. Age; sex; color; exposure to the elements; scars from burns (particularly from radiation); keratoses, (both of the senile and seborrheic varieties and those caused by arsenic); cutaneous horns; chronic ulcers, and trauma may all be contributing factors in the development of carcinoma.

While epithelioma may occur at almost any age, the great majority of such lesions are found in people over forty; Elliott and Welton¹ found that of 1742 cases of epithelioma, 27.7 per cent were in patients between the ages of 50 and 59—almost the same proportion reported by Ziesler,² 123 out of 461 were between the ages of 51-60. As age increases, the incidence of epithelioma increases.

Cancer is more commonly found in men than in women; of Elliott and Welton's 1742 patients, 57.4 per cent were male and 42.6 per cent were female.

The color of one's skin is an important factor in the development of cancer. The fair blond type which sunburns and freckles easily is especially apt to be subject to such growths of tumors. It is interesting that carcinoma is frequently found in the white areas of Hereford cattle, and on the white lids of the Longhorn Texas cattle. The darker the skin, the less likely one is to have cancer of the skin; for example, it is exceedingly rare to find a skin cancer in one of the Negro race.

Exposure to sun over a long period of time is believed to be one of the chief factors in producing skin cancers. In the Southern states the incidence of cancer on the exposed parts in individuals in rural sections.

especially farmers, is very high. Every spring I have a number of patients returning with deeply tanned skins from a winter in Florida, who come in with keratoses and skin cancers, chiefly on the face. Dr. Robert R. M. McLaughlin, in a personal communication, stated that the incidence of cancer in young men in the service who had been stationed in the South Pacific was frequent, particularly cancer of the lips. Sigmund Peller,³ of Johns Hopkins University, and Charles S. Stephenson, of the U. S. Navy, found that skin and lip cancer occurred eight times more frequently in males in the U. S. Navy than in civilian population in same age group.

Lt. Commander G. A. Robinson,⁴ in charge of the Radiology and Tumor Service, U. S. Naval Hospital, Long Beach, California, states that the incidence of keratosis and epithelioma in young naval personnel on South Pacific duty was very great. He states that blisters, fissures and hyperkeratoses precede cancer of the lip. The term "South Pacific" lip has been given to these lesions.

Skin cancer in old x-ray burns is very common. I have found that the probability of cancer increases with the age and the severity of the burn, and I believe that in 80-85 per cent of those having x-ray burns, a skin cancer will develop within 20 to 25 years, if the burn is on the exposed parts.

Skin cancer is also found sometimes in the scars of burns from other sources, particularly if the scars are in areas easily or frequently irritated. Most of us are aware of cancer at the site of pressure of glasses on the bridge of the nose, and from senile keratoses and so-called "liver spots," which appear on the face from age plus exposure.

Seborrhea, with a chronic scaling and a redness of the eyebrows and the groove between the wings of the nose and cheeks, often results in epithelioma.

Practically all patients with Xeroderma pigmentosa develop skin cancer on the exposed parts, particularly the face. Keratoses and cornified warts caused by arsenic frequently become carcinomatous, usually of the squamous cell type. These are not to be confused with the multiple superficial basal cell epitheliomas, which appear on the trunk—these also are attributable to arsenic.

Chronic ulcers of long standing, such as those due to tuberculosis, trophic ulcers, ulcers in sclerodermiac conditions—and, rarely, varicose leg ulcers may be the site of squamous cell carcinoma. Cutaneous horns

usually become carcinomatous and often of the metastasizing variety.

When we analyze the foregoing facts it immediately becomes evident that one must protect the aging skin by the exercise of proper hygiene, which consists of a thorough cleansing of the skin with water, wash-cloth and a fatty soap (cold cream, Castile or lanolin soap), the use of a suitable cream several times a day and the application of a protective, bland powder. It is imperative that the skin be protected from over-exposure to sun and winds.

It has been my observation that the women who spend a great deal of time on the care of their complexions and hands rarely, if ever, are troubled with skin cancers or pre-cancerous conditions. Too, in this day of constant smoking—even by women—it may be that the protecting lipstick accounts for the infrequency of cancer of the lip in women.

The greatest safeguard against the development of cancers in x-ray burns is the excision of the scar where it is possible. Large areas which cannot be treated surgically should be kept carefully cleaned with fatty soaps and creams, as suggested above for senile skins. In addition, all keratoses and dilated blood vessels should be removed by the electric needle, thereby reducing the development of cancer in these burned areas.

Every endeavor should be made to heal all chronic ulcers. Scars should have gentle massage with cream, and, where possible, tension and all friction of scars should be eliminated. Senile keratoses, collections of dilated blood vessels and all arsenical keratoses should be removed, preferably with the electric needle, in order to safeguard the skin against cancer.

Treatment: Practically 100 per cent of all skin cancers of the basal and squamous cell variety can be cured if removed early in their development, regardless of the method of treatment employed—provided it is *thorough*. Undoubtedly there are some lesions better suited for treatment by one procedure than by another, but I have always considered the choice of the method secondary to that of the thoroughness with which it is done. Tragedies resulting from basal and squamous cell carcinoma of the skin are always due to neglect or to inadequate treatment. Each time a skin cancer recurs after removal the greater the difficulty of treating it successfully. Furthermore, the chronic irritation oftentimes produced by improper treatment of a basal cell epithelioma produces an additional skin cancer of the squamous or metastasizing

type, so that the patient has two growths to contend with, and he is in a much more serious condition than he would have been without treatment.

To illustrate, a few years ago a well-known surgeon brought me a patient with inoperable carcinoma of the skin, who had been through successive methods of treatment for eleven years. The lesion had begun as a small, wartlike keratosis just above the right eyebrow—this the Doctor had curetted and cauterized. When the lesion recurred six months later it was taken off with an electric needle. The third recurrence was treated by a radiologist with radium. The fourth was treated at a well-known cancer hospital, where he had an operation, followed by radiation. Later he spent some time in Paris, and was treated with radium at the Curie Institute. He then returned to New York and consulted an eminent cancer expert at a cancer hospital. Both in Paris and in New York the doctors assured him that sequestra of bone, which came out of the superorbital wound, was due to the necrosis of the bone from radium, and that he had no cancer. The lids of the right eye were closed with a dark red, firm, brawny swelling, and a pencil could be introduced an inch or more into the hole beneath the right eyebrow. Red, granular, warty tissue was around the ulcer. The diagnosis of carcinoma was obvious, and a radical surgical operation was advised. Of course, the primary lesion was only a keratosis which could have been effectively and easily removed if it had been done thoroughly.

I see so many instances of a similar character that I have become convinced that the average physician regards cancers and pre-cancerous conditions of the skin too lightly, and does not treat such lesions thoroughly enough. The foremost consideration of every physician should be the complete removal of every cancerous growth, regardless of the resulting scar. For many years I have made it a practice to remove skin cancers with the electric needle, first taking a piece for biopsy study, then following with thorough desiccation of the lesion and beyond the border, removing the charred or desiccated material with a curette or scalpel. I repeat this procedure until I feel I have gone well beyond the diseased borders. I then give 1800 R in three divided doses.

My results in cases which had had no previous treatment have been, so far as it has been possible to follow, approximately 100 per cent successful, as far as a return of the growth is concerned.

Elliott and Welton treated 1052 cases of basal and squamous cell

carcinoma—some without previous treatment and others with—using the combined method of the electric needle, curettage and radiation, and they report that 97.1 per cent had cures for five years or longer. That is a remarkable and encouraging result.

Treatment of Melano-Carcinoma: The best protection against melano-carcinoma is to remove thoroughly all pigmented moles situated at sites where they might be subjected to irritation. This removal can be accomplished safely with the electric needle.

The only cases of metastatic melano-carcinoma arising from moles which I have seen have followed either surgical excision or cauterization with acids. For example, a thirty-six year old physician consulted me, stating that six months previously a surgeon had excised a dark colored mole from the back of his right shoulder. A few months later a walnut-sized gland appeared in the right axilla following a few days of strenuous golfing. He had had fever 102° , general malaise and considerable discomfort in the swollen gland. He was relieved of his discomfort in twenty-four hours by radiation, his gland subsided to almost normal and his temperature fell. Within three weeks two or three hazelnut-sized glands were felt in the same axilla; biopsy of one showing melano-carcinoma.

Any blue nodule or papule in the skin, of recent development, should be deeply and widely excised at the earliest possible opportunity. Even then it is doubtful that metastasis may be prevented, and especially is this true of lesions which may appear on the buttocks, the sole of the foot, around the nail or on the glans penis, as I saw in a case a few weeks ago. Metastasis in such cases takes place early, possibly with or even before the appearance of the nodule. The prognosis of melanoma in infancy or childhood is much more favorable.

Summary: The prevention of epitheliomas is best accomplished by exercising proper care of the skin; by removing all known irritants which give rise to some pre-cancerous condition; by avoiding continuous or over exposure of the skin to the sun or sun lamps; by careful treatment of x-ray burns, keratoses of all types; by avoiding long and excessive use of arsenic compounds.

Epitheliomas of the skin can be successfully removed if treated early enough and with thoroughness. The selection of the method of removal is secondary to the complete eradication of all cancerous growth.

All pigmented moles which show changes in surface markings, or

become irritated, or are situated in locations likely to be subjected to irritation should be removed carefully and completely, preferably with the electric needle.

Melano-carcinomas must be removed immediately by wide and deep excision.

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It is announced by The New York Academy of Medicine that a sum of \$1,500 is available during 1947, under the Edward N. Gibbs Memorial Prize for original research in diseases of the kidney.

Candidates must be physicians, who have been graduated at least three years and are residents of the United States. Candidates shall submit evidence of research, already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney.

Applications, with the required evidence, should be addressed to The Gibbs Prize Committee at The New York Academy of Medicine, prior to March 31.

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APRIL 1947

THE EXCRETION OF WATER *

HOMER W. SMITH

New York University College of Medicine, New York, N. Y.

IT is well established that the renal excretion of water is in part under the control of the antidiuretic hormone (ADH) of the pituitary gland. This hormone serves to promote the reabsorption by the tubules of water from the glomerular filtrate, and to produce a minimal flow of maximally concentrated urine, the lower limits of flow and the upper limits of concentration being determined by the presence in the urine of unreabsorbed solutes, such as salt, urea, etc. It is equally well established (if frequently forgotten) that the secretion of ADH is controlled by hypothalamic centers, notably the supraoptic nuclei, and that through reflex connections with other neural centers the secretion of this hormone may be influenced by a variety of sensory stimuli, by excitement and by conditioned reflexes. Within the kidney itself, the urine flow is related, however distantly and complexly, to the rate of filtration, a renal function which is fairly static in man, but in the dog, and even more so in the rabbit, is susceptible to wide fluctuations.

Thus the rate of water excretion by the kidneys is subject to so

* This is the first of three lectures delivered under the Morris Herzstein Lectureship at the University of California and Leland Stanford University, San Francisco, California, December 2, 4 and 6, 1946.

many conditioning factors that changes in urine flow are sometimes very difficult to interpret. For over a century the rate of urine excretion was about the only thing the renal physiologist could measure, and we can sympathetically commiserate with our colleagues on their careful graphs in which V , the rate of urine flow, was plotted against T , the elapsed time of the experiment, to produce a picture that in the end was about as meaningful as a cross section of the Sierra Nevada mountains.

Against this variability in the rate of water excretion, there arise a number of major questions: How does the body keep itself in water equilibrium when water excretion is susceptible to so many disturbing factors? What factors determine the lower limits of water excretion, and why does water excretion during extreme water diuresis not rise to the upper limit set by the rate of glomerular filtration, namely, to about 130 cc. per minute, instead of rising to a maximal rate which is only about one-eighth of this value? And what do we mean by water equilibrium? What relations exist between the excretion of water and of salt, what mechanisms exist in the kidney to maintain the concentration of sodium (or total base) of the body constant and to govern the distribution of this base between chloride and bicarbonate? And how is the volume of body fluid, specifically of the extracellular fluid, regulated?

I do not presume to be able to answer all these questions, but our understanding of the excretion of electrolytes has progressed rapidly of late and I believe that it is possible at least to frame the questions with experimental data more accurately than has hitherto been possible.

In the past ten years renal physiology has passed from a qualitative to a quantitative stage, and not the least important of its quantitative advances has been the development of reliable methods for measuring the rate of glomerular filtration. We have learned that the average filtration rate in man is about 130 cc. per minute, and that out of this relatively large quantity of fluid no more than 10 or 15 per cent is ever excreted as urine, either during maximal water diuresis or in complete diabetes insipidus. Within this narrow range of 10 to 15 per cent residual water available for urine formation, variations in urine flow appear to be controlled largely if not wholly by variations in the secretion of the antidiuretic hormone. Some years ago I was led by these facts and by other evidence to distinguish what I called the 'obligatory'

from the 'facultative' reabsorption of water.¹ It was posited that the obligatory reabsorption of water, accounting for some 80 per cent or better of the glomerular filtrate, occurred in the proximal tubule in association with the reabsorption of electrolytes, glucose, etc., and that facultative reabsorption, by which variations in urine flow are effected under the control of ADH, occurred in the distal tubule. There are now reasons, which I will detail later, to challenge this view as possibly an oversimplification.

That a considerable fraction of the filtered water is reabsorbed in the proximal tubule, however, has been experimentally verified by Walker, Bott, Oliver and MacDowell,² who have applied the exquisite micropuncture technique, originally developed by Walker and Richards, to the study of tubular reabsorption in the guinea pig and rat. These investigators found that creatinine is progressively concentrated as the urine passes down the proximal tubule, in such a manner that by the end of this segment its U/P ratio would be about 5.0. This would mean that 80 per cent of the glomerular filtrate has been reabsorbed, leaving 20 per cent to be passed on to the thin limb of the loop of Henle and to the distal system. It is particularly to be noted that Walker and his coworkers believe that some constant fraction (*ca.* 12.5 per cent) of the glomerular filtrate is reabsorbed by each 10 per cent length of proximal tubule, so that the overall fraction reabsorbed by the end of the tubule is relatively constant and independent of the rate of filtration in the attached glomerulus. Allowing for further water reabsorption in the thin limb, it is reasonable to suppose that some 87.5 to 90 per cent of the water may be reabsorbed in these two segments, raising the U/P ratio to 8 or 10, before the urine enters the distal tubule. The maximal urine flow attainable in water diuresis or diabetes insipidus in dog or man represents roughly the complementary fraction (some 12.5 per cent), which might mean either that the remainder is reabsorbed in the distal tubule under the influence of ADH, or that an equivalent fraction fails to be reabsorbed proximally in the absence of ADH. This represents a major question into which we will inquire further.

It is known that hypertonic urine is formed only in the birds and mammals, the only classes of vertebrates in which the thin segment of the loop of Henle is present, and when Burgess, Harvey and Marshall³ found that increased tubular reabsorption of water is induced by ADH

only in the birds and mammals, they suggested that this hormone acts on the thin segment. Since the urine becomes hypertonic under the influence of ADH, it has been generally supposed that this hormone specifically accelerates the reabsorption of water against osmotic pressure; but to assign osmotic work to the low epithelium of the thin limb, as opposed to the higher epithelium of the distal tubule, presents difficulties, and, though little has been said on the subject, I think most investigators have been inclined to the interpretation that the locus of action of ADH, and of osmotic work, is restricted to the distal tubule.

Shannon⁴ has shown that the diabetes insipidus dog, in the entire absence of ADH, is capable during dehydration of elaborating a moderately hypertonic urine; one infers that ADH serves directly or indirectly, depending on its locus of action, to facilitate or accentuate this intrinsic tubular process, with the result that in the normal animal, where the supraopticohypophyseal system is intact, slight degrees of dehydration lead to a minimal excretion of a hypertonic urine, thus giving forcible control to water conservation.

In the experiments of Walker *et al*² the urine throughout the length of the proximal tubule remains isosmotic with the plasma, and their evidence is convincing that the proximal tubule cannot make a hypertonic urine. One important consequence issuing from this conclusion is that when any unreabsorbed substance is introduced into the glomerular filtrate (mannitol, sucrose, excess glucose, urea, etc.) it will by its osmotic pressure reduce the proximal reabsorption of water and thereby increase the load of water delivered to the distal tubule. Whether the proximal tubule can make a hypotonic urine is a matter which I think must be left open. I say this despite the fact that Walker *et al* found the urine to be hypotonic to the plasma in only two of twenty-one instances, but the conditions of their experiments—among other circumstances, the fact that most of their animals were infused with saline or sucrose before and throughout the period of observation—were perhaps not such as to favor the production of a hypotonic urine.

There is an upper limit to the maximal concentration of the urine, more or less characteristic of different species and perhaps even of different individuals, and presumably attributable to the reabsorptive capacity of the distal segment. Investigators have long searched for the factor or factors which determine this concentration ceiling; the present evidence, in which the experiments of McCance and his coworkers⁵

weigh heavily, indicates that there is but one limiting factor, and that is the osmotic pressure of the urine, whether the dominant solute is sodium chloride, sodium bicarbonate or urea. Accepting this or some modified definition of the limiting concentration of the urine, it follows that during oliguria or any other condition where ADH secretion is maximal, the urine flow will tend to increase or decrease with the load of osmotically active solutes left over after proximal tubular reabsorption, and therefore (with proper qualifications in respect to proximal tubular reabsorption) with the load of osmotically active solutes delivered to the tubules by the glomerular filtrate. Under such conditions, if glomerular activity varies the urine flow will tend to increase or decrease in a parallel manner, even though the final urine volume is only a small fraction of the glomerular filtrate. Small doses of sodium chloride, mannitol, urea, etc. will tend to increase the urine flow by increasing the distal osmotic load, and metabolic changes induced by variations in endocrine activity and the like, may through the increased excretion of sodium chloride or urea have comparable effects. I do not think such changes in urine flow, which reflect changes in osmotic load, should be called diuretic without qualification, since they have a wholly different explanation than does definitive diuresis induced by water. They could better be described as osmotic diuresis.

A second factor which has sometimes been conceived as influencing minimal urine flow is what I may call the velocity effect. Shannon^{4,6} suggested that the time during which the urine is exposed to the distal tubules may play a role in determining the amount of water reabsorbed. He utilized this interpretation in connection with the excretion of electrolytes in the diabetes insipidus dog because he noted that during osmotic diuresis induced by glucose in a dehydrated dog the osmotic pressure of the urine falls, i.e., it is only about one-sixth of the maximal value normally observed under comparable conditions of dehydration. It is as though the excess glucose discharged from the proximal tubule carried with it into the distal tubule such a flood of water that time was not available for osmotic equilibrium to be attained. However, the concentration of water in the tubules is virtually constant and maximal, regardless of the composition of the urine and the rate of urine flow and it is difficult to see how the rate of flow *per se* could influence amount of water reabsorbed. McCance and his coworkers have observed that sodium chloride diuresis in dehydrated rats is similarly accompanied

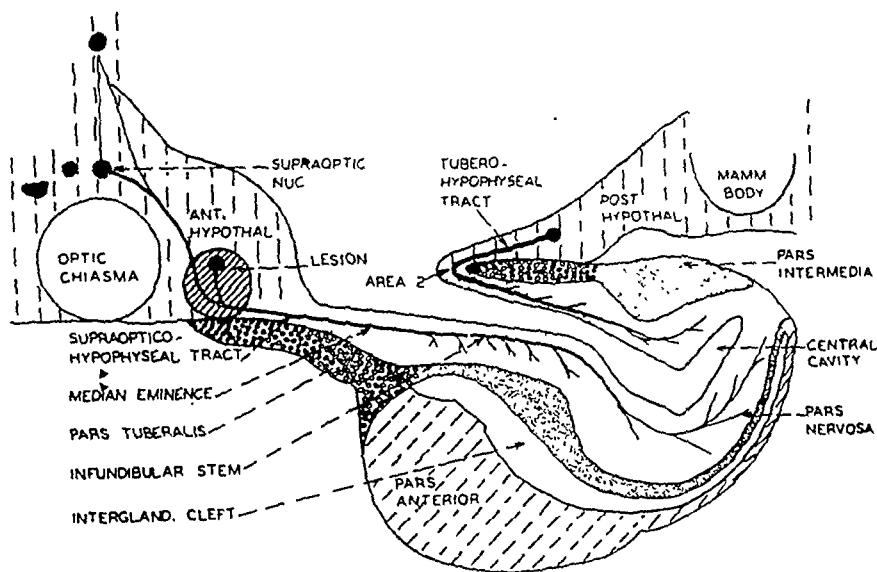


Figure 1. The anatomy of the pituitary gland in the rat. The indicated lesion is the one 'essential for the production of diabetes insipidus.'¹⁰

by a fall in urinary osmotic pressure by one-half; reduction in osmotic pressure also occurs during sodium chloride diuresis in man, and more recently they have demonstrated it again with sucrose.^{7, 8, 9} They suggest that the inverse relationship between urine volume and maximal osmotic pressure implies a constant quantity of osmotic work (whereby the product urine volume x osmotic pressure equals a constant) though they have not as yet presented a definitive demonstration of this relationship.

On ADH itself I need say only a few words, since the subject has been recently reviewed by Pickford¹⁰ and Verney.¹¹ A considerable degree of order has now emerged from what a few years ago was a state of chaos—as Fisher, Ingram and Ranson remarked in their monograph, *Diabetes Insipidus*, “the history of diabetes insipidus reads like a comedy of experimental errors.” But as a result of the studies of Verney, Pickford, Richter, White, Ranson and their coworkers, and many others, a description of the supraopticohypophyseal mechanism can now be given which will satisfy the majority of investigators. The mammalian hypophysis (Figure 1) consists of a neural division and a glandular division, the first separable into the median eminence, infundibular stem and pars nervosa, the second into the pars tuberalis, pars intermedia and pars anterior. The so-called posterior lobe, a term which

Fisher *et al* discard because of its ambiguity, is made up of the pars nervosa of the neural division and the pars intermedia of the glandular division. It is in the pars nervosa that ADH is elaborated. The pars nervosa receives nerve fibers from perhaps several hypothalamic nuclei, but chiefly from the bilateral supraoptic nuclei, which nuclei give their name to the supraopticohypophyseal tract. Any circumstance, and only such circumstances, as will destroy bilaterally the supraoptic nuclei or interrupt the supraopticohypophyseal tract, or destroy the neural tissue of the infundibular stem and median eminence as well as the pars nervosa, will wholly destroy the capacity to secrete ADH; in the absence of this hormone (except in marked dehydration, when the intrinsic activity of the distal tubules comes into play), the urine flow rises to the limit set by 'obligatory' reabsorption (we return the word to quotation marks since it must be used tentatively); i.e., to about $\frac{1}{8}$ th of the glomerular filtrate, or in man to some 16 cc. per minute or 23 liters per day. Such is the circumstance in experimental diabetes insipidus and such is essentially the condition during maximal water diuresis, when secretion of ADH is in abeyance. In water diuresis, as in diabetes insipidus, in the dog and in man, there is no *necessary* change in the filtration rate or renal blood flow^{11 18}—the whole matter concerns the reabsorption of that residue of water left over from the 'obligatory' process.

ADH is distinct from the oxytocic and amphibian water-balance principles, which are secreted by the neural division, and from the melanophore principle, which is secreted by the pars intermedia.¹⁹ It occurs in all classes of vertebrates²⁰ though only the mammals and to a lesser extent the birds can elaborate a hypertonic urine.

ADH is immediate and constant in its action, which is best revealed by the arrest of diuresis following a standard dose of water in a well hydrated animal. Administered intravenously its effects wear off in 30 to 40 minutes. Its essential mode of action is the direct effect upon the reabsorption of water by the renal tubules, an effect which is quantitatively related to the logarithm of the dose.²¹ The increased excretion of chloride, long associated with ADH, is probably attributable to small quantities of pitocin in commercial preparations;^{16, 22, 23, 24} the choluretic action of pitocin itself is possibly not a specific effect upon chloride reabsorption in the tubules but referable to changes in filtration rate. Minimal urine flow in hydrated dogs is obtained by the intra-

venous administration of about 5.0 milliunits per hour, a dose far smaller than is usually used by experimentalists, but true minimal urine flows are obtained only by a combination of dehydration and hormone secretion—for in the latter condition the filtration rate is decreased, thus decreasing the delivery of electrolytes and water to the proximal and hence to the distal tubule.^{4,6}

Most investigators agree that the normal stimulus inducing secretion of the antidiuretic hormone is an increase in the osmotic pressure of the plasma,^{25, 26} but whether this acts upon the supraoptic nuclei or on other neural centers is not determined. Verney's¹¹ recent experiments indicate that the osmoreceptors are reached by the internal but not the external carotid artery. The supraoptic nuclei, it may be re-emphasized, have such far-flung connections that a large variety of stimuli can influence neurohypophyseal secretion.^{11, 27, 28} Ether and chloroform anesthesia induce increased hormone secretion, either by a 'release' phenomenon or by stimulating the supraopticohypophyseal system; morphine is particularly potent in this respect and all the barbiturates are in some degree effective.²⁹⁻³² It was the use of anesthetized animals that led Magnus and Levy, who first studied the effects of pituitary extract on urine formation, to assert, falsely we now know, that such extracts have a diuretic action. I would not labor these points were it not for the fact that there is still evident a tendency to attach unwarranted significance to changes in urine flow, to base upon such changes the alleged discovery of a new hormone, or a new specific inducing tubular diuresis, or, without recourse to readily available measurements, to infer from them changes in filtration rate.

I have thus far discussed the factors, so far as they are known, which determine the upper and lower limits of water excretion within the bracket of 'facultative' reabsorption, i.e., throughout the course of water diuresis. Osmotic diuresis presents a somewhat different problem and cannot be resolved without better knowledge of the excretion of electrolytes and of the relations between proximal and distal water reabsorption.

~~—~~We may now turn to the meaning of water equilibrium. The most fundamental consideration here is the fact that water moves freely between all parts of the body, by way of the circulating plasma, and distributes itself in such a manner that the effective osmotic pressure of the three major osmotic compartments of the body, the plasma, the

extracellular (or interstitial) fluid compartment and the intracellular compartment, is the same except in so far as differences are maintained dynamically by differences in hydrostatic pressure or tissue pressure. However, the mere fact that water is, in the osmotic sense, uniformly distributed throughout the body does not place any limitation upon the actual volume of water, or of isotonic fluid, contained within any one of these three compartments, since the number of osmotically active constituents in each can and does vary more or less independently. Between the extracellular fluid and the plasma water moves in accordance with the balance of forces between the hydrostatic pressure of the blood in the capillaries and the oncotic pressure of the plasma proteins. Between the extracellular fluid and the tissues, water moves along gradients determined largely, if not entirely, by osmotic forces. Water and electrolytes are always being added to the body or subtracted from it, moving from plasma to extracellular fluid or in the reverse direction, as the organism departs from or approaches equilibrium.

In the extracellular fluid, the principle osmotically active constituent is sodium chloride, though more exactly we should speak of the total base with its chief attendant anions, chloride and bicarbonate. The constancy of the total base and its physiological significance in body fluid regulation have been recognized ever since Gamble, Ross and Tisdall³³ reported on this subject nearly 25 years ago, and it is to be regretted that in recent years it has received scant attention. Opposed to the osmotic activity of these non-penetrating electrolytes is the osmotic activity of the tissue electrolytes, chiefly potassium and magnesium. The concentration of the intracellular constituents, which seem to be fairly rigidly confined, is presumably determined by the cellular protein which gives to the cell its fixed characters. It seems probable that it is the quantity of osmotically active material in the cell which constitutes the point of reference in the regulation of the osmotic pressure of the extracellular fluid.

It has been said that the effective stimulus to the osmoreceptors of the supraopticohypophyseal system appears to be the osmotic pressure of the extracellular fluid. It seems probable that the osmotic pressure of this fluid is significant primarily in reference to the more stable osmotic material in the cell. In this view, the maintenance of intracellular osmotic pressure is the crux of water regulation. When the required intracellular osmotic pressure is attained, specifically in these osmoreceptors,

water equilibrium is reached. (This view does not allow for the slow exchange of electrolytes or of other osmotic constituents between cells and the extracellular fluid which may lead to adaptation, or for diffusion gradients and other secondary factors, and must be looked upon as a tentative and skeletonized statement.)

Water equilibrium can be attained at any volume of the extracellular fluid, large or small, and we are therefore forced to believe that a mechanism exists for the conservation or excretion of total base, and particularly sodium, which operates more or less independently of the mechanism for conserving water, and specifically in relation to the volume of the extracellular fluid, for otherwise the quantity of sodium in the body, and hence the volume of extracellular fluid, could expand or contract indefinitely.

Before we seek to explore this question further, however, let us recall that in the renal conservation of water, there is a division of labor between the proximal and distal tubule. It is to be anticipated that in the renal reabsorption of electrolytes a similar division of labor will throw the bulk of reabsorption on the proximal tubule. Proximal reabsorption may be looked upon as a sort of internal circulation within the kidney which stems from the glomerular filtration-tubular reabsorption pattern of that organ, and which has nothing to do with the finer control of water and electrolyte conservation.

But upstream to the renal tubule is the glomerulus, designed to pour both water and electrolytes into the nephron in a flood which is quantitatively out of all proportion to the needs of the organism to excrete either. I never cease to marvel at the extravagance of this operation: in man the water filtered per day amounts to some 180 liters, or more than three times the total body water, of which only one or two liters are excreted; the total sodium chloride filtered amounts to nearly 1200 grams, of which only some 5 to 10 grams are excreted; the total sodium bicarbonate amounts to some 400 grams of which only 200 mg. are excreted. The ratio of filtration to excretion is thus roughly 100, 200 and 2000 to 1, a proportion which warrants the use of the term extravagant.

Apart from the fact that the process of urine formation starts with this seemingly superfluous flood of water and electrolytes requiring tubular reabsorption, what specific role do the glomeruli play in water and electrolyte balance? In the frog the administration of water is ac-

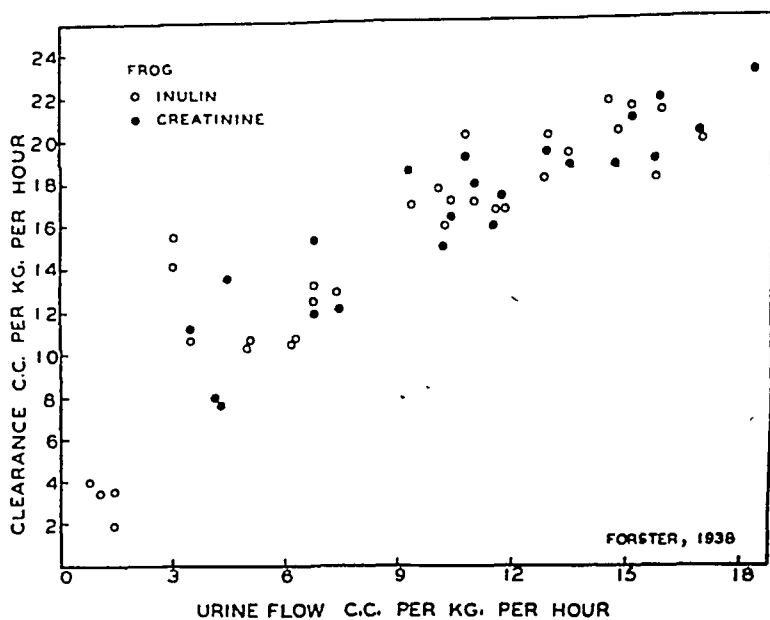


Figure 2. Relations between glomerular filtration rate and urine flow in the frog.²⁴

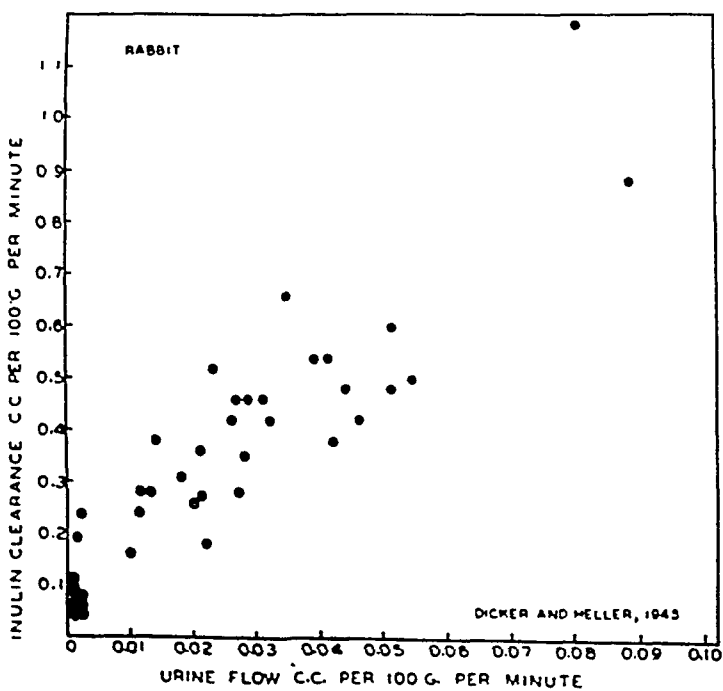


Figure 3. Relations between glomerular filtration rate and urine flow in the rabbit.²⁵

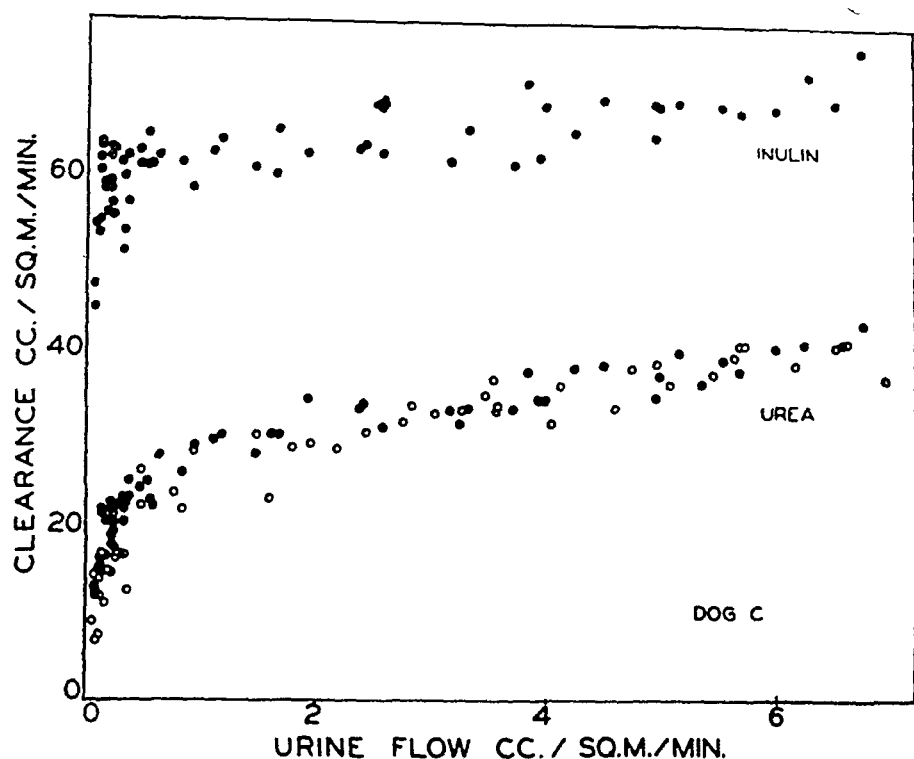


Figure 4. Relation between glomerular filtration rate and urine flow in the dog.³¹

accompanied by a marked increase in the filtration rate (Figure 2); by the glucose saturation method, Forster³⁴ has shown that this increase in filtration rate is attributable to an increase in the number of active, or fully active, glomeruli. During oliguria glomerular activity is reduced to a very low level. One may suppose that variable glomerular activity represents a primitive method of regulating the urine flow, and hence water excretion, since the antidiuretic hormone accelerates the tubular reabsorption of water only in the birds and mammals, the only forms in which a hypertonic urine is formed.³ Whether this relationship is primitive or not, it is strikingly evident in the rabbit, which behaves almost like the frog in that hydration provoking an increase in urine flow is accompanied by an increase in filtration rate^{35, 36, 37} (Figure 3). With the possible exception of the marine seal, which has not been carefully examined with respect to water diuresis, the rabbit is the only recorded mammal that shows this phenomenon.

(It is worth noting parenthetically that the recent report of Trueta and his colleagues^{38, 39} on the continued perfusion of the renal medulla

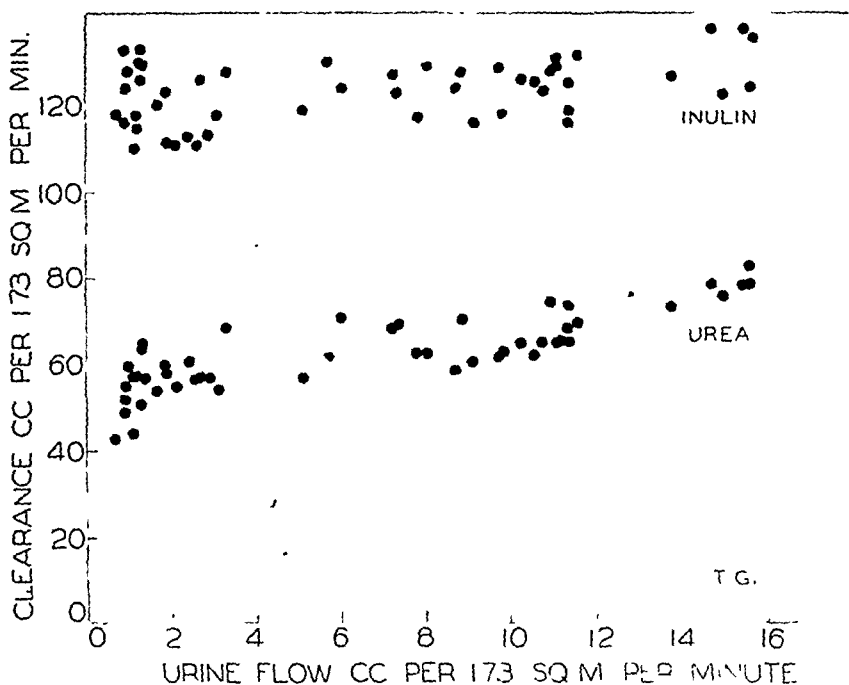


Figure 5. Relation between glomerular filtration rate and urine flow in man.¹²

during cortical ischemia produced by tourniquet shock is apparently based solely on rabbits (the species is not named but rabbits are designated in their preliminary report), and if such is the case the observations need to be confirmed in other species. With the glomerular circulation in the rabbit so labile, it is possible that *vasa rectae* and other glomerular by-passes are of greater importance in this species than in other animals.)

In the dog, however, the filtration rate is essentially independent of hydration except at extremes of dehydration or excessive hydration⁷ (Figure 4). Yet it is well demonstrated that glomerular filtration is a relatively labile function in the dog: it can be reduced by severe dehydration,^{4,6} and increased in normally hydrated animals by 50 per cent or more by the administration of saline,^{4,6,40} saline possibly being more effective than water in this respect because water is distributed throughout the body tissues, whereas saline is confined to the extracellular compartment. Shannon inferred that these changes in glomerular activity reflect and probably are initiated by changes in the volume of the extracellular fluid, an inference that does not exclude reduction of the

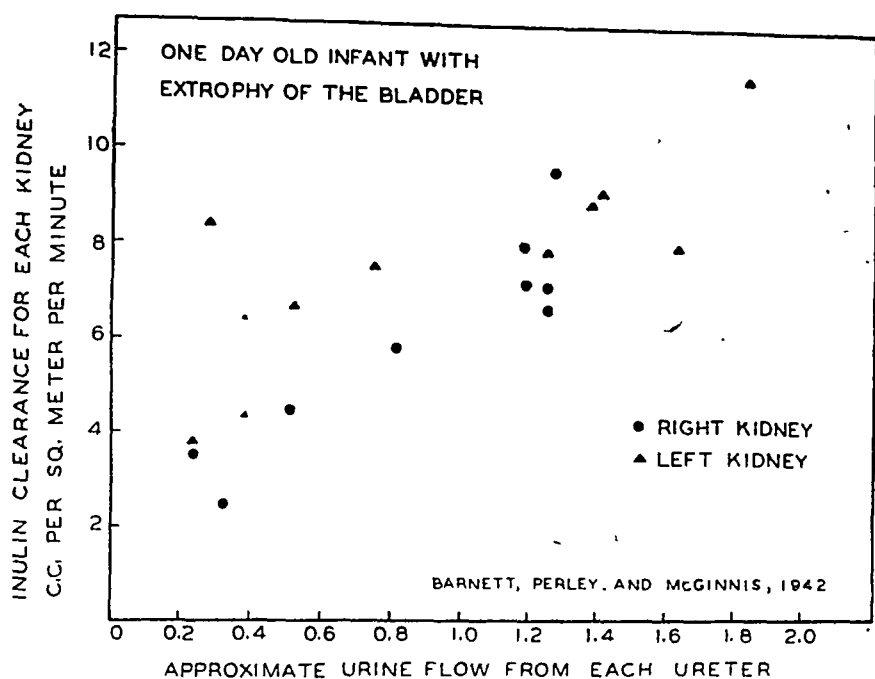


Figure 6. Relation between glomerular filtration rate and urine flow in a one-day old human infant.⁴³

oncotic pressure of the plasma proteins, or in viscosity by dilution of the red cells, as factors that will increase the effective glomerular pressure. The overall magnitude is such, however, as to indicate that the glomerular apparatus itself is involved. The dog also shows a substantial increase in filtration rate on a high protein diet, and a substantial decrease on a low protein diet,^{41, 42} the effects of protein being imitated by amino acids and certain other metabolites.⁴³ Here the changes in glomerular activity are certainly mediated by the glomerular-vascular apparatus.

Dicker and Heller's³⁶ report on the rat shows that in respect to hydration this animal resembles the carnivorous dog, rather than its rodent cousin, the rabbit. Why these species differences exist remains a puzzle and more studies in comparative physiology are needed to clarify this important problem.

Even more stable than in the dog, the filtration rate in the adult human kidney (Figure 5) is not specifically related to hydration¹² and changes only moderately after the administration of saline⁴⁴ or during excessive dehydration.^{8, 45} As judged from the urea clearance, it changes very little with changes in the protein content of the diet,^{46, 47, 48} al-

though children are more susceptible to protein intake.⁴⁹ In respect to hydration, however, young infants behave like rabbits, the filtration rate increasing markedly with urine flow⁵⁰⁻⁵³ (Figure 6). This functional relationship appears to be associated with the inactivity of the glomeruli during fetal life, and we need to know more about the specific adaptations peculiar to placental reproduction before we can think of it as primitive and harkening back to our tadpole ancestry.

I want to emphasize here, not the relative stability of the filtration rate in the adult human, but the fact that it can and does vary under conditions not yet defined. This variability is much greater in the dog, and most remarkable in the rabbit. The fact of this variability immediately raises questions concerning glomerular-tubular balance, for it is now well established that in many instances the reabsorptive capacity of the tubules is sharply limited. Such limitations have been demonstrated (in the dog or in man) in the tubular reabsorption of glucose,^{54, 55} phosphate,⁵⁶ amino acids,⁵⁷ creatine,^{57, 58} and vitamin C.^{59, 60} In each of these instances, however, the plasma concentration of the substance in question is determined by equilibria between the plasma and some organ other than the kidneys (the liver, in the case of glucose and amino acids, the bones in the case of phosphate, etc.), the kidneys serving only as a retaining dam to prevent wasteful excretion at normal plasma levels; only at elevated plasma levels is the tubular reabsorptive mechanism saturated and the excess glucose, phosphate, creatine, etc. allowed to escape from the body. The role of the kidneys here is merely one of a safety valve. Moreover, the maximal rate of reabsorption of the substances named is, with the possible exception of phosphate and creatine, of such an order of magnitude that, at normal plasma levels, an increase in the filtration rate within the normal range does not impose upon the tubules a load in excess of their reabsorptive capacity and the filtered material remains completely or almost completely conserved.

The situation is, however, very different with electrolytes. There is no credible evidence that any organ in the body can store sodium chloride or sodium bicarbonate, or can secrete them or otherwise participate in the regulation of their plasma concentration. Setting aside secondary disturbances (water and electrolyte shifts between the plasma and tissues, the secretion of the enteric fluids, etc.), the regulation of the plasma concentration of these electrolytes is solely and continuously a renal responsibility, as much as it is in the case of water. Clearly, if

the renal tubules are to be charged with conserving or rejecting some small fraction of the filtered sodium chloride and sodium bicarbonate, the absolute magnitude of the filtration rate will be a matter of great importance.

SUMMARY

The reabsorption of water by the renal tubules may be divided into two clearly separable processes which, until better terms suggest themselves, may be called the obligatory and facultative processes. Obligatory reabsorption accounts for some 80 to 87 per cent of the glomerular filtrate and most of this may be referred to the proximal tubule, while facultative reabsorption accounts for the remainder.

Facultative reabsorption is under the control of the antidiuretic hormone (ADH) of the neurohypophysis. Whether facultative reabsorption is to be referred to the distal tubule or the thin limb of the loop of Henle remains open to question, but it is within this bracket that variations in urine flow must be adjusted to keep the body in water equilibrium. The maximal urine flow in water diuresis or diabetes insipidus cannot exceed the facultative fraction (some 13 per cent, at a minimal U/P ratio of 8) of the filtration rate. The minimal urine flow is conditioned by the load of water and osmotically active solutes delivered to the distal tubule, the precise osmotic limitations on distal water reabsorption being unknown.

The secretion of the antidiuretic hormone from the neurohypophysis is under the neural control of the supraoptic nucleus. The effective stimulus eliciting an increased secretion of this hormone is an increase in the osmotic pressure of the blood. The osmoreceptors, as yet unidentified, are probably located in the central nervous system. The action of the antidiuretic hormone, so far as positive evidence is available, is confined to the promotion of water reabsorption by the renal tubules.

Water moves freely between all the fluid compartments of the body, and water equilibrium is apparently attained when the osmotic pressure of the extracellular fluid is balanced against the fixed osmotically active constituents of the osmoreceptors of the neurohypophyseal system. Water equilibrium can be attained at any volume of the extracellular fluid, and the control of the volume of the extracellular fluid is a problem distinct from the conservation of water itself.

Glomerular activity, which determines the supply of water and electrolytes to the renal tubules, is intrinsically variable, though the degree of variation differs markedly in different species, as well as between the infant and the adult. Since the renal tubules are solely responsible for the retention of both water and electrolytes, the maintenance of an appropriate balance between glomerular and tubular function is a matter of considerable importance in the problem of body fluid regulation.

(To be continued)

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PHARMACOLOGY OF STREPTOMYCIN*

HANS MOLITOR

TO most clinicians streptomycin meant as recently as one year ago scarcely more than another antibiotic with theoretically interesting properties; today, however, this agent has advanced to a position second only to that of penicillin. With the difficulty of large volume production already overcome and ample supplies freely available, it is safe to predict that in the physician's armamentarium this drug will soon become a tool of first importance.

Any drug, which is reasonably safe and possesses activity against such common diseases as tuberculosis, *E. coli* and *Salmonella* infections, is bound to be widely tried. There are probably only two obstacles which at this moment may keep streptomycin from being used in far more cases than justified on the basis of present evidence: its cost and the necessity of frequent administration by the parenteral route. With streptomycin, as with penicillin, the initial cost of the product was of necessity high. However, with improvements in production methods the cost has already been materially reduced and it seems not unreasonable to expect that this trend will continue; and as far as the mode of administration is concerned, it is hoped that by improvement in the pharmaceutical forms of the drug the inconvenience of repeated parenteral administration may be surmounted, similar to the development that has taken place with penicillin.

In view of the anticipated wide use, it seems therefore timely to present a description of the pharmacological and toxicological properties of streptomycin, particularly since in its presently available form this drug may cause certain undesirable side-reactions.

At the onset, I should like to state that the information given today is somewhat different from that believed to be correct one or two years ago. Having participated in the pharmacological study of streptomycin since its very beginning and having presented the results of such

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studies on several previous occasions, I have become particularly aware of these changes. To give you a brief example: In May 1945, in one of the first reviews of the pharmacology of streptomycin, nausea, headache, flushing of the skin and occasional fainting spells were listed as the most common side-reactions; in January 1946,¹ the statement could be made that these effects were due to an impurity which in the future would be removed in the process of manufacture. Mention was made at that time, however, of another, and more serious, side-effect, consisting of disorders in the vestibular and auditory system. These effects, first observed in man by Hinshaw and Feldman² and in animals by our group, were then believed to be an intrinsic property of streptomycin. Now it has again become necessary to modify these views.

These frequent changes lie not in faulty experiments or a hasty interpretation of the results, but rather are due to the fact, that the drug available today is quite different in purity from that supplied experimenters one or two years ago.

These differences, however, manifest themselves only in a change of the toxicological reactions and do not effect the chemotherapeutic properties. Therapeutic results obtained with a given number of streptomycin units of one of the early preparations, which rarely exceeded a purity of 25 per cent in terms of the active principle, are reproducible by the same number of streptomycin units of one of the later batches, which are 70 to 95 per cent pure. There are, however, very definite variations in the type, frequency and severity of side-reactions observed with samples of different purity.

Like penicillin, streptomycin at the time of its discovery and first investigation was a rather crude mixture, containing in addition to the active principle a multitude of contaminants, some of them inert, others pharmacodynamically highly active. While the absolute quantity of these impurities varied with individual batches, their qualitative properties remained essentially the same, as long as the conditions of manufacture were not changed. In view of this it was permissible to speak of "standard" impurities, to be expected in all commercial preparations of a similar type of manufacture; indeed, the specifications of the Food and Drug Administration recognized the presence of these impurities, and permitted their presence up to a certain, moderate degree. The latter provision was made because a complete exclusion of some of these frequent contaminants would, at that time, have reduced the

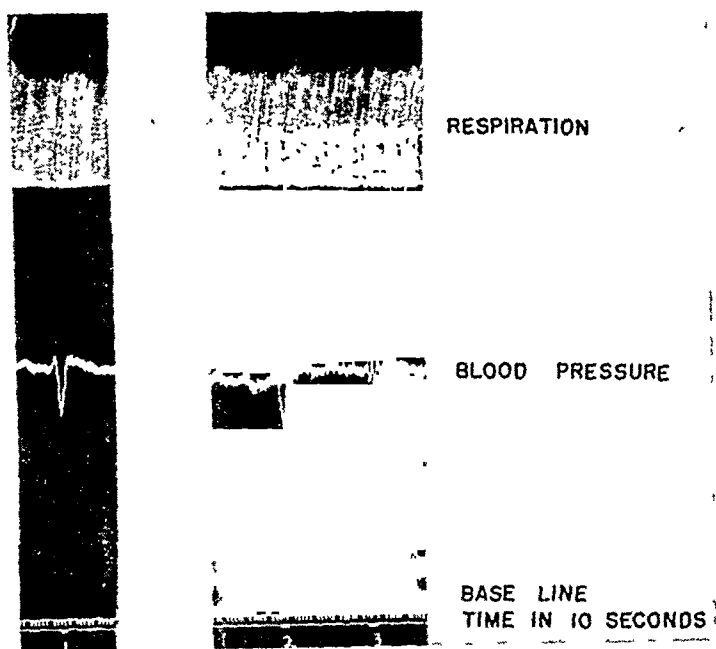


Figure 1. Blood pressure effect before and after histaminase treatment. Cat 3.25 kg. nembutal anesthesia 35 mg/kg. subcutaneously.

1. Histamine hydrochloride 1.00005 mg/kg.
2. Streptomycin concentrate lot 206, 50 units/kg.
3. Streptomycin concentrate lot 206, histaminase treated, 50 units/kg.

output of the much needed drug too severely. Side-reactions described in the earlier clinical papers need therefore not necessarily be expected with today's preparations, even though the therapeutic claims remain unaffected. Indeed, because a several-fold larger dose of streptomycin preparations of greater purity may be administered with impunity, it is possible to obtain today favorable results in cases where the use of one of the earlier streptomycin preparations might have failed, due to limitation of the maximum tolerated dose.

Among the pharmacodynamic effects that can be produced in animals by the administration of excessive doses³ and that are partly due to impurities, are the following:

1. *Circulatory Effects.* These were histamine-like and consisted in animals of peripheral vasodilatation, fall of blood pressure, increased secretion of gastric juice, temporary inhibition of water diuresis and contraction of the isolated intestine and uterus. Since histaminase, an enzyme specifically destroying histamine, abolished these effects, they

must be ascribed to an impurity closely related to, or identical with, histamine. This impurity has now been completely removed, at least in the material examined in our laboratory (Fig. 1).

In man, this impurity was responsible for such reactions as headache, nausea, vomiting, reddening of the skin, and occasionally, fainting spells, which occurred not infrequently with the early, impure material, particularly when it was injected intravenously at a rapid rate. It was found that the incidence of these reactions in man was proportional to the blood pressure lowering effect of the same lots in animals and it seems therefore reasonable to expect that with the elimination of this impurity the occurrence of clinical side-reactions of this nature has become a matter of historical interest only.

2. *Hepatic Changes* consisting in fatty metamorphosis and degeneration, may be produced in animals with very large doses. No such changes have been observed in man.

3. *Renal Effects* such as albuminuria, hematuria and appearance of casts are due to glomerular and tubular degeneration and necrosis; they are reversible, if administration of the drug is stopped in time. In man, severe effects of this nature have been observed only with one of the earliest samples; however, an appearance of casts, without albuminuria, does not seem to be infrequent, particularly when the urine is acid. It has been, however, transitory and not of serious consequence, in any instance thus far recorded.

The renal and hepatic effects of streptomycin depend largely upon the purity of the sample used, but even highly purified material may produce them in animals provided extremely large doses are given.

4. *Neurotoxic Properties.* Hinshaw's original observation of a labyrinthine disturbance in patients repeatedly receiving large doses of streptomycin has been confirmed by other clinical investigators. The use of accurate tests for vestibular and auditory function has shown, that it is more frequent than was originally assumed, for patients quickly learn to compensate for the vestibular dysfunction and notice its presence only when blindfolded or in the dark. The auditory effect, which apparently requires still larger doses of streptomycin, may result in a marked loss of hearing, particularly for the high frequencies. The vestibular effect can be produced in dogs and rabbits and persists for a long time after discontinuation of treatment. It may become irreversible if the streptomycin administration is not terminated.

TABLE I—COMPARISON OF DOSES NECESSARY TO PRODUCE NEUROTOXIC SYMPTOMS

Influence of Mode of Administration on Dose and Time Required for Neurotoxic Signs				
	Route	Units Per Kilogram Per Day	First Appearance of Neurotoxic Signs	Total Dose Units per kg.
Dogs	I.M.	100,000	20 Days	2,000,000
	I.C.	1000 (1 Dose)	Within 1 Hour	1000
Rabbits	S.C.	300,000	11 Days	3,300,000
		450,000	7 Days	3,150,000
	I.C.	1000-1250 (1 Dose)	Within 1 Hour	1000-1250

In animals the neurotoxic reactions were first produced by repeated intramuscular injections of large doses (100,000-200,000 units per kg.). The relatively long interval of 1 to 2 weeks between the administration of the first dose and the appearance of vestibular dysfunction made it difficult to compare quantitatively the degree of neurotoxicity of individual lots and to decide whether this phenomenon was an intrinsic property of streptomycin, one of its "standard" impurities, or a combination of both. My associate Kuna and myself therefore tried to produce neurotoxic signs by intracisternal injection, following the procedure employed by Walker and his associates⁴ in their investigation of the neurotoxic properties of penicillin. We found that as little as 1000 units of streptomycin per kg., injected in this manner, produced within 30 to 60 minutes essentially the same effects as the daily intramuscular injection of the same lots in doses of between 100,000 to 300,000 units over a period of at least 10 days (Table I).

Using the technique of electrical recording of ocular movements, my associate Hawkins⁵ found, in rabbits receiving streptomycin for a period of 7 to 14 days, that the first sign of chronic, vestibular involvement is a change in the nystagmus in reference to rotation. This change appears 2 to 3 days before disturbances in the animal's gait and posture are obvious. The rate of the rhythmical ocular movements during and after rotation is decreased; ultimately rotation may fail to elicit more than an occasional deviation of the eye.

RELATIONSHIP BETWEEN NEUROTROPIC AND INTRAVENOUS TOXICITY OF STREPTOMYCIN IN ANIMALS AND MAN

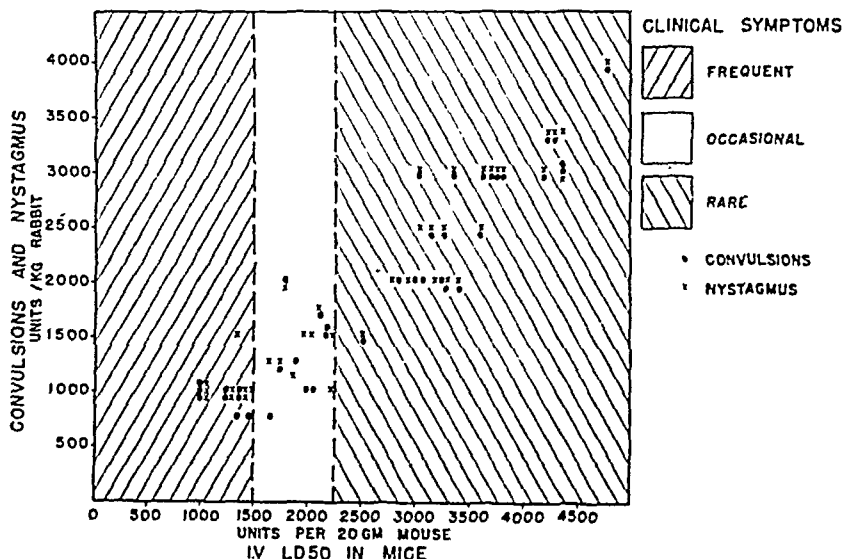


Figure 2. Relationship between neurotropic and intravenous toxicity of streptomycin in animals and man.

Utilizing the technique of intracisternal injection, we compared a large number of streptomycin samples, including many of an early date of manufacture, and determined the number of units necessary to produce in 50 per cent of the animals spontaneous nystagmus. We found not only more than five-fold differences among different batches of streptomycin, but noted also an apparent parallelism between the neurotropic (intracisternal) and general (intravenous) toxicity in animals and the tolerance of the same lots in man (Fig. 2); the latter, however, could not be ascertained for all samples, and the parallelism between neurotoxicity in experimental animals and in man is therefore only suggestive. However, even if we disregard such a possible relationship between the acute toxicity in animals and the tolerance in man, the fact nevertheless remains that wide differences exist among the neurotoxicity of individual lots and that the unit potency of an individual lot is not directly related to its neurotoxicity. These findings strongly suggest that the neurotoxic effects of streptomycin are due, at least in part, to an impurity. Whether the factor responsible for acute death by respiratory failure and determined by intravenous injection in mice is identical with that causing specific neurotoxic non-fatal effects, remains at this

time an open question.

Thus at least two of the serious clinical side-effects of streptomycin may largely, if not solely, be caused by impurities. There are, however, other occasional clinical reactions, such as skin rashes, temporary elevation of body temperature, pain in the joints, and discomfort at the site of injection which cannot yet be reproduced in animals and make it therefore difficult to decide whether they are caused by impurities or are allergic manifestations; the fact that they fail to occur regularly makes it rather unlikely that they constitute intrinsic properties of the drug. At least one of these effects, viz. discomfort at the site of injection, seems to be largely due to impurities since it is far less pronounced with material of greater purity.

The pharmacodynamic effects of streptomycin just described were obtained with samples of varying purity, some as low as 10 per cent, others at least as high as 97 per cent, when evaluated by standard methods. It is quite possible that the small fraction unaccounted for in the latter may be pharmacodynamically inert; however, until a 100 per cent pure streptomycin is available or the exact nature of the remaining impurities is known, it will be impossible to decide with certainty which of the pharmacodynamic effects observed are intrinsic properties of the drug. Based on our present knowledge, however, it would appear, that absolutely pure streptomycin will in large doses depress the medullary centers; that in animals acute death following intravenous injection of extremely large doses will be caused by respiratory failure; that doses within the therapeutic range will not produce serious systemic toxic effects, except a depression of the vestibular and auditory centers; and that pure streptomycin will be free from untoward local reactions. These predictions are based on extensive pharmacological and clinical studies of the most highly purified materials available at this time, material which already conforms with most of these properties.

As with other chemotherapeutic agents, the mode of administration and the dosage regime are most important for the success of streptomycin treatment. For this reason it may be in order to summarize the data on absorption and excretion obtained in experimental animals.

Streptomycin, which is readily soluble in aqueous media, is rapidly absorbed when injected subcutaneously, intramuscularly and intravenously and produces peak concentrations in the blood within as little as 45 minutes after subcutaneous injection and 30 minutes after intra-

SERUM CONCENTRATION OF STREPTOMYCIN FOLLOWING THE VARIOUS METHODS OF ADMINISTRATION

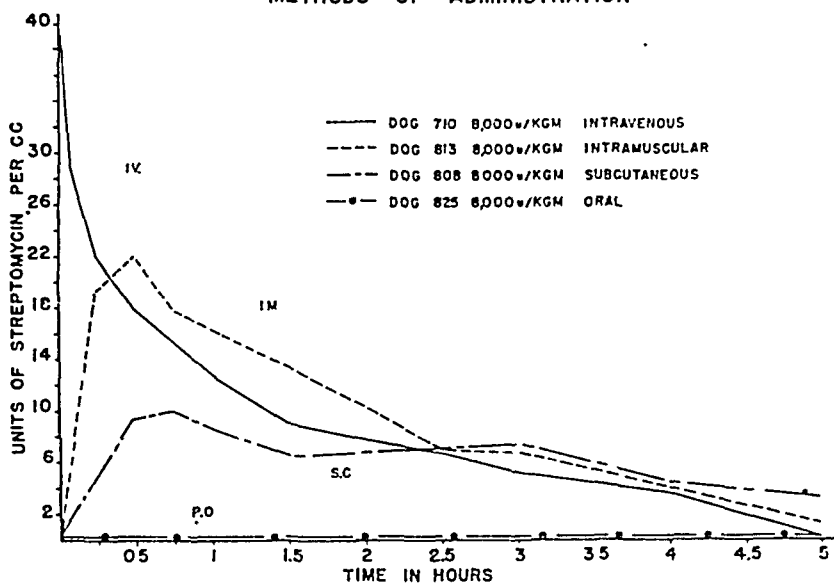


Figure 3. Serum concentration of streptomycin following the various methods of administration.

SERUM CONCENTRATION OF STREPTOMYCIN IN MICE

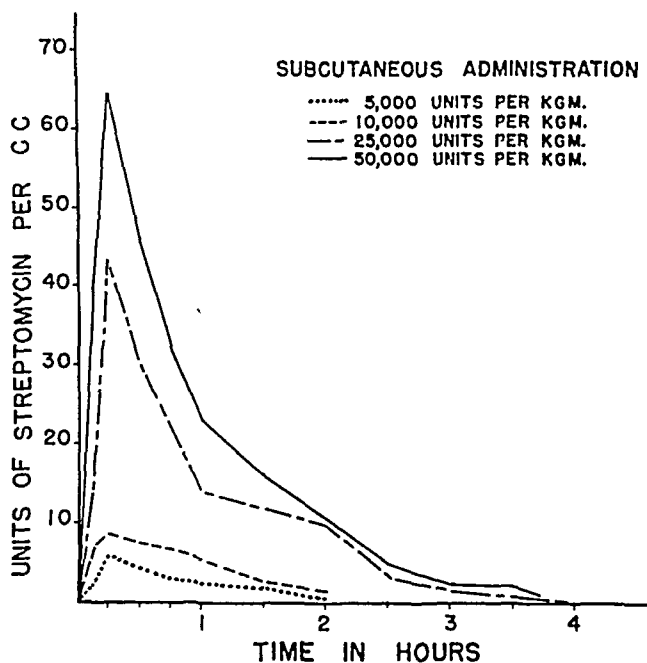


Figure 4. Serum concentration after streptomycin doses of increasing magnitude.

STREPTOMYCIN CONCENTRATION IN C.S.F.
AND SERUM AFTER INTRA-CISTERNAL
INJECTION OF 3000 μ OF STREPTOMYCIN
PER KILOGRAM OF RABBIT

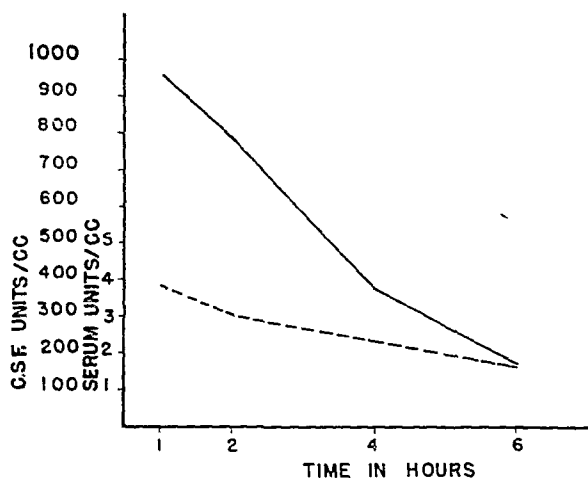


Figure 5. Streptomycin concentrations in cerebrospinal fluid and blood.

muscular injection (Fig. 3). These high concentrations, however, persist only for a relatively short time. As expected, an increase in the dose results not only in a higher peak, but also in a prolongation of the therapeutically effective concentrations in the blood (Fig. 4). For best results repeated administration at frequent, relatively short intervals (3-4 hours) is essential.

The therapeutically effective concentrations vary considerably with the type of organism as well as the individual strain and range from approximately 6 units per cc. for tularemia, which is highly sensitive to streptomycin, to a minimum of approximately 25 units per cc. for less sensitive pathogens such as *Salmonella* or typhoid.

The amount of streptomycin absorbed after oral administration is too low to affect most organisms; rectal administration, either in form of a microclyster or suppository, produces similar unsatisfactory results. However, the factors influencing the rate of absorption with this mode of administration are not yet sufficiently understood; results are quite erratic, occasionally giving high and well sustained drug concentrations while at other times producing mere traces of the drug in the blood of the same animal without apparent reason. The fact, however, that under certain, not yet controllable conditions, completely adequate absorption

from the rectum may occur, indicates that further investigation of the factors governing absorption from the intestinal tract eventually may render this mode of administration reliable.

Intrathecal and intracisternal injection of streptomycin results in a high concentration in the spinal fluid, but only limited diffusion into the general circulation (Fig. 5). Since the reverse is equally true and the streptomycin concentrations in the cerebrospinal fluid after intravenous injection are rather low, it seems justified to combine intrathecal and intravenous administration whenever a high concentration in the cerebrospinal fluid is needed. However, when using this route it should be remembered that in animals acute neurotoxic reactions may be induced by the intracisternal injection of only a fraction of the dose likely to produce them with other modes of injection. Furthermore, for this type of therapy only material of the highest purity should be used since the impurities contained in less purified material are likely to aggravate the neurotoxic reactions.

While the oral administration of streptomycin fails to produce a therapeutically significant concentration in the blood, the very fact that the drug is not absorbed from the gastrointestinal tract may prove useful in cases where control of the bacterial flora in the intestinal tract is desired. Experiments performed on animals have shown that peroral administration of streptomycin results in a marked reduction in the total count of intestinal bacteria. It would therefore seem justified to make use of the powerful antibacterial action of streptomycin in the preparation of patients for abdominal surgery, using relatively small doses by mouth for 24 to 48 hours before operation and continuing for an equal period postoperatively.

The development of streptomycin resistant strains is undoubtedly one of the most serious obstacles in the prolonged use of this antibiotic. Drug-fastness may develop within a few days and may result in a several thousand fold decrease of the sensitivity of the bacteria to the drug.⁶ Experiments in our laboratory by Graessle⁷ have indicated that, in line with the earlier work of Carpenter,⁸ a combination of the antibiotics streptomycin and penicillin may appreciably retard the development of drug-fastness. However, the most promising way of avoiding this complication is, at this time, the administration of initial doses sufficiently large to effect immediate and complete elimination of the pathogenic microorganisms. In view of the wide variations of bacterial

strains in sensitivity to streptomycin it is therefore highly desirable to determine, first, the relative susceptibility of a given strain and then adjust the streptomycin dose accordingly; it goes without saying, that a mode of administration and a dosage regime must be selected, which will insure the maintenance of an optimal drug concentration at the desired site of action.

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THERAPY OF ERYTHROBLASTOSIS
FETALIS WITH EXCHANGE TRANSFUSION*

A. S. WIENER, I. B. WEXLER, and T. H. GRUNDFAST

THE first exchange transfusions on infants were performed more than twenty years ago. In fact, in our search of the literature we were surprised to discover a report of a case in which the therapy had been used with success in 1925 for treating an infant with icterus gravis. In this case, reported by Hart,¹ the infant was the result of the eighth pregnancy, had a birth weight of eight pounds and was not jaundiced at first. The seven preceding children had all been born alive, but six of these died following the development of jaundice. On the fourth day of life, jaundice developed in the infant in question, and an exchange transfusion was decided upon in order to "remove enough toxins from the blood to prevent progress of the disease." According to Hart, the method had been brought out and perfected by the late Bruce Robertson while J. L. McDonald performed the actual procedure; 300 cc. of blood were withdrawn from the longitudinal sinus and 335 cc. of donor's blood were injected into the saphenous vein together with 60 cc. of 5 per cent glucose solution. The next day the jaundice was less intense and by the fourth day completely gone and the infant's general condition appeared very much improved. Jaundice reappeared when the child was three weeks old but disappeared spontaneously four days later.

Despite the spectacular success of this first case there is no indication that the procedure was taken up by other workers or even again by Hart himself. Perhaps the operation proved technically more difficult or more hazardous than is suggested by the description in the original article. In addition, lack of knowledge of the role of the Rh factor in the pathogenesis of the disease probably resulted in unfavorable results in subsequent cases.

Our own experiments with exchange transfusions in infants were started in 1944 when we used a technique similar to that described by

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Hart, though we were not aware of the existence of his paper at that time.² In an experiment performed on an infant with mongolian idiocy, we succeeded in effecting a 90 per cent substitution by withdrawing and injecting 275 cc. of blood. The infusion offered no obstacles but coagulation interfered with the withdrawal of blood, although we tapped in succession the femoral veins, the longitudinal sinus, and a radial artery. When we subsequently applied the method to an infant with icterus gravis, coagulation of the baby's blood caused us to terminate the procedure when only 50 cc. had been withdrawn and 120 cc. injected. The condition of the infant, furthermore, was so good at birth that the treatment seemed to us to be more dangerous than the disease. As happens much too often in such cases the infant subsequently died with kernicterus, and in retrospect there is reason to believe that it could have been saved by a more thorough exchange transfusion.

We planned to carry the work further and considered the use of heparin* as an anticoagulant to facilitate the withdrawal of blood. In 1946, Wallerstein⁴ took up the procedure again and performed exchange transfusions in infants, using the technique of Hart. At this time Dr. Peter Vogel⁵ informed us that he had succeeded in performing an exchange transfusion by first heparinizing an erythroblastotic infant, and we resumed our experiments. By regulating the dose of heparin, using the saphenous vein for the infusion and the radial artery for bleeding we were able to effect a 90 per cent exchange in an infant with mongolian idiocy by infusing 500 cc. of blood and withdrawing 400 cc. simultaneously.⁶ This procedure went much more smoothly and rapidly than did our original experiments and convinced us of its safety. Among other things the relatively enormous amount of citrate injected caused the infant no obvious embarrassment.

It is evident that it is never possible to effectuate a complete substitution of the patient's blood by the donor's because the infusion and bleeding must be done concurrently. As we have shown,⁶ if an amount of Rh-negative blood equal to twice the volume of the infant's blood is injected and withdrawal of an equal amount simultaneously carried out, a substitution of approximately 90 per cent will result.**

* Purified heparin had been used successfully by Thalheimer et al.³ in experimental exchange transfusions in dogs.

** In a newborn infant with an approximate blood volume of 250 cc., about 500 cc. of blood should be injected and simultaneously withdrawn. The magnitude of such an operation can be appreciated when it is pointed out that a comparable procedure in an adult would entail the transfusion of about 10,000 cc. of blood; so that as many as twenty blood donors would be required. Our main experience with large exchange transfusions in adults has been in cases of hemorrhage in which enormous quantities of blood were lost and had to be replaced by transfusion. In one patient, a man with a bleeding duodenal ulcer, as much as 5500 cc. of blood had to be injected before the bleeding was controlled by operation.⁷ In a second, more recent case, a woman with an abdominal pregnancy, 7000 cc. had to be transfused before the bleeding was finally controlled. Both patients recovered uneventfully.

The success or failure of this procedure will now depend upon the fate of the remaining 10 per cent of the infant's own Rh-positive red cells. If this residuum is eliminated by lysis, no harm will result. But should the cells clump and block the circulation no beneficial effect will have been obtained. While in our earlier cases whole citrated blood was used, an unfavorable experience in one case, which we ascribe to intravascular *conglutination* of the residual 10 per cent of the infant's Rh-positive blood, has caused us to modify the procedure in subsequent cases by removing one-half of the donor's plasma and replacing this with saline in order to reduce the *conglutinin* content. Furthermore, whereas in our earlier cases our practice was to inject 100 cc. more than was withdrawn, we have subsequently narrowed this margin to less than 50 cc., in order to avoid the danger of producing a polycythemia. When the blood count is high the viscosity of the blood is increased and the circulation slowed, producing conditions favorable to intravascular clumping.

Obviously, while an exchange transfusion will as a rule arrest the course of the disease, it cannot correct tissue damage that has occurred before treatment is instituted. For this reason it is important to treat the infants as soon after birth as possible. Routine antenatal Rh tests are of great value in indicating ahead of time which infants may require exchange transfusion.

A preliminary report of our experience with our first two cases treated by exchange transfusion has already appeared.⁸ Subsequently, we accumulated considerable hematological and clinical data concerning these two patients and we now propose to present a full report. In one case the maternal serum contained univalent Rh antibodies (*glutinins*); in the other, bivalent Rh antibodies (*agglutinins*) were present in high titer. Our report will therefore illustrate the contrasting effects of the two varieties of antibodies, and will also act as a standard of reference for subsequent papers in which our experiences with other cases will be described.

CASE 1. Mrs. M. L., 32 years of age, came under the care of one of us (T.H.G.) in February, 1946. She had had one previous pregnancy in 1943 which was complicated at term by placenta previa. She was delivered by Cesarean section of a normal female infant, weighing 6 lbs., 10 oz., who is alive and well. At the time of this operation, the mother was given a transfusion of 500 cc. of whole blood and made an uneventful recovery. She returned during her second pregnancy, and routine Rh tests showed her to be Rh negative and sensitized to the Rh factor, while her husband was Rh positive.

(Case 1 continued on page 210)

In view of these findings, a complete study was carried out on the entire family with the results shown in Table I.

TABLE I
RESULTS OF GROUPING AND Rh-Hr TESTS IN CASE 1

<i>Blood of:</i>	<i>Group and Subgroup</i>	<i>M-N Type*</i>	<i>Rh-Hr Type</i>
Father	A ₁	M	Rh ₁ Rh ₂
Mother	A ₁	MN	rh
Daughter	A ₁	MN	Rh ₁ rh

* The M-N types are not important clinically, but are given for the sake of completeness.

Tests for Rh antibodies on the mother's serum gave the following results:

Agglutination Test—Negative

Coagulation Test—Positive (12 units)

These findings indicated that the patient was sensitized to the Rh factor, with antibodies of the univalent variety—the type of antibody which in high titer usually gives rise to hydrops, and in low titer to viable infants with hemolytic anemia.^{9,10} Since the husband belongs to type Rh₁Rh₂, he was almost surely homozygous for the Rh₂ factor, so that every child of this couple would normally be expected to be Rh positive (either type Rh₁ like the daughter, or type Rh₂). Thus, we could be reasonably certain that the fetus which the patient was carrying was erythroblastotic. Since the titer of the maternal antibodies was moderate, there was a good chance of obtaining a viable infant.

The patient having had a previous Cesarean section, this constituted an indication for an elective repeat Cesarean section. This made it possible to select a definite date for the delivery, and two weeks before term seemed to be a favorable time from the standpoint of both mother and fetus.

On the morning of the day chosen for the section, 500 cc. of group A, type rh blood* were drawn from a professional donor and mixed with 60 cc. of citrate solution. The mother was delivered at the Jewish Hospital on September 14, 1946 by a low-flap Cesarean section under fractional spinal anesthesia. It was noted that the amniotic fluid was yellow and the umbilical cord bile stained. The patient was a male with a birth weight of 6 lbs., 9 oz., who appeared slightly pale but had a lusty cry. His liver and spleen were not palpable.

The exchange transfusion on the infant was started immediately.** An incision was made at the ankle, a blunt 20 gauge cannula inserted into the saphenous vein, and the infusion of blood started. The radial artery on the opposite side was exposed at the wrist. Then, 0.2 cc. (200 units) of heparin† was injected into the saphenous vein. The radial artery was nicked and the infant's blood allowed to flow freely through the opening. By this time, approximately 75 cc. of the donor's blood had run into the saphenous vein.

(Case I continued on page 212)

* Since both parents belonged to group A, the expected infant had to be either group A or group O. If the infant proved to be group A, it would be unwise to completely replace its blood with group O blood because the anti-A agglutinin in such a large quantity of donor's blood might harm the infant; obviously such an infant would have to receive A blood. Group A blood would also be acceptable even if the infant belonged to group O. The reason for this is that whatever antibodies an infant has at birth are derived from the mother, so that the expected infant in our case could not have any alpha antibodies.

** Though blood specimens were taken for laboratory examinations, the procedure was not delayed pending the reports.

† This was provided through the courtesy of the Upjohn Company.

TABLE II
RESULTS OF HEMATOLOGIC STUDIES IN CASE 1

	At birth	4 hrs.	2nd day	3rd day	4th day	5th day	6th day	7th day	10th day	14th day	25th day	34th day	40th day	59th day	82nd day	Time when test was made																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													

During the entire procedure it was attempted to keep the infusion approximately 50 to 75 cc. ahead of the bleeding in order to allow a margin of safety. The heparin injection was repeated two more times—the last (third) injection being given at approximately the middle of the procedure, with the idea that the heparin effect would then be nullified by the time the transfusion was completed. The bleeding was so free that it was necessary to apply pressure intermittently to the radial artery in order to permit the infusion to keep pace with it.* After a total of 430 cc. of blood had been obtained, the radial artery was doubly ligated and the skin sutured. The infusion was continued until the entire 560 cc. of citrated blood had run in. At the end of the procedure, it was noted that the infant appeared bloated and lethargic, and its precordial impulse seemed rapid and weak. That these symptoms were due to overloading of the circulation was supported by the observation that the spleen had become markedly enlarged. Apparently some miscalculation had occurred, because we now found the infant's weight to be 7 pounds, that is, 7 oz. above birth weight. The infant responded well to stimuli, and since the plethora did not appear to cause him excessive embarrassment, he was sent to the nursery.

The infant's course in the hospital was observed closely clinically and by daily hematological examinations, the results of which are given in Table II. The blood smear taken immediately after birth showed marked abnormalities of the erythrocytes, with anisocytosis, frequently polychromatic macrocytes, and 69 nucleated R.B.C. per 100 W.B.C. In the grouping tests on the infant's blood before transfusion, reactions corresponding to group A, type M, type rh' were obtained. However, when two drops of the baby's blood suspension were placed in a test tube, centrifuged, the supernatant fluid removed and replaced by a drop of compatible oxalated adult plasma, clumping (conglutination) occurred upon further incubation in the water bath. This proved that the infant's erythrocytes were coated with univalent Rh₀ antibodies and that it really belonged to type Rh₁ and not to type rh'.**

Four hours after the exchange transfusion, a blood count showed that the hemoglobin concentration had risen to 117 per cent with an R.B.C. count of 5.36 million per cmm. At this time the infant appeared quite well and active, and the spleen seemed slightly smaller. The subsequent course in the hospital was essentially uneventful. There was a gradual decline in the R.B.C. count and hemoglobin concentration, but on the 10th day, these were still within normal limits. The nucleated R.B.C. disappeared from the smears by the fifth day, at which time reticulocytes also became scanty. The cord serum had an icterus index of 35 units, but jaundice was not noticeable clinically until the second day and then only on the face. It was most noticeable between the fourth and sixth days and then gradually receded, at no time being at all pronounced. Differential agglutination tests on the infant's blood immediately following the transfusion showed that a replacement of approximately 90 per cent had been accomplished. The infant's own remaining cells soon disappeared so that after the seventh day, its blood reacted as A₁MN rh, that is, the type of the donor.

As a matter of interest, the maternal Rh antibodies were titrated following the delivery in order to determine whether a Cesarean delivery stimulates an antibody rise like a normal delivery. A three-fold increase in titer was observed, indicating that during Cesarean delivery, a shower of fetal cells probably enters the maternal circulation, just as in birth per vaginam. Thus, Cesarean delivery does not protect the mother from becoming sensitized.

The infant's subsequent course was uneventful. There was the usual period of apparent aplasia, so that the blood count gradually declined as the donor's erythrocytes

(Case I continued on page 213)

* In subsequent cases we permitted the bleeding to continue unchecked and speeded up the infusion with the aid of syringe and 3-way stopcock. In this way the procedure could be completed in a shorter time (60–90 minutes).

** Similar observations on erythroblastotic infants have been reported by one of us (W.) previously.^{11, 12}

disappeared from the circulation. At the age of one month, the hemoglobin concentration was still 80 per cent. Reticulocytes appeared on the blood smear at the end of the fifth week, at which time the hemoglobin concentration was only 56 per cent. If one assumes that the amount of blood administered was sufficient to give the infant a hemoglobin concentration of 100 per cent and that the survival period of the transfused erythrocytes in newborn infants is 12 weeks, then in a five week period during which there is no regeneration, we would expect the blood hemoglobin concentration to drop to seven-twelfths of 100 per cent or to about 58 per cent. The observed hemoglobin concentration of 56 per cent is very close to that expected under this hypothesis.*

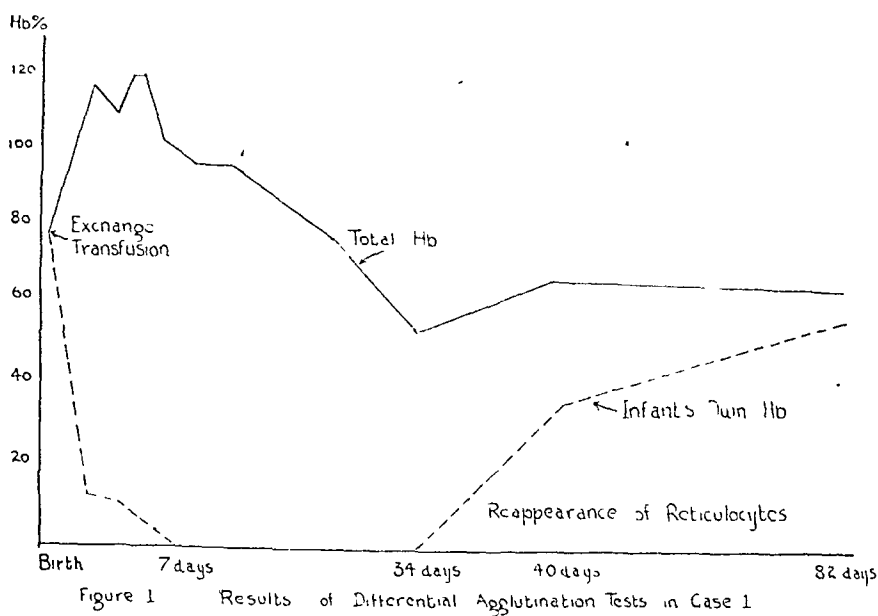
Following the appearance of reticulocytes in the blood smear, the blood regeneration not only kept pace with, but even exceeded, the rate of destruction of the donor's red cells so that by the sixth week the hemoglobin concentration was 65 per cent. At that time the differential agglutination tests clearly revealed the presence of the infant's own Rh-positive red cells. By the end of the third month all the cells in the circulation were Rh positive. Throughout the course, the infant appeared and behaved perfectly normal except for the jaundice during the first two weeks of life.

The advantage of the exchange transfusion in this case was that it did away with the need for repeated transfusions and it spared the infant's body the task of getting rid of the products of hemolysis. Of course, its most important purpose was to preclude the possibility of intravascular conglutination.

In Figure 1 we have summarized the most important hematologic findings of Case 1. The resemblance between this figure and one previously published² in connection with a case of erythroblastosis fetalis (hemolytic anemia variety) treated by simple transfusions with Rh-negative blood is striking. The reason for this is that in that earlier case we accomplished what really amounted to a complete exchange transfusion. The circumstances in that case were very similar, the mother having had a previous erythroblastotic infant delivered by Cesarean section and the husband being homozygous Rh positive (type Rh₁Rh₂). Five hundred cc. of blood were drawn from group O, type rh professional donor in preparation for an exchange transfusion, but when the infant was delivered by Cesarean section, she proved to be already practically exsanguinated, due to a severe hemolytic anemia. An immediate transfusion of 160 cc. of the blood revived the infant and subsequently 75 cc. more were administered. In this way, a complete exchange transfusion was accomplished, though we were spared the task of bleeding the infant.

As Figure 1 demonstrates, the curve of elimination of donor's erythrocytes from the infant's body is practically linear. The reason for

* Since infants grow rapidly during the neonatal period, their blood volumes also increase relatively rapidly. In the presence of bone-marrow aplasia, this factor alone could cause a gradual decline in the blood count. This may also account for our observation that transfused red cells appear to survive only three months in infants, in comparison with a maximum survival period of four months for adult recipients.



this, as was first pointed by one of us,^{13, 14} is that the blood obtained from the donor is actually a mixture of red cells of all ages. Naturally, the older cells wear out earlier and disappear first from the recipient's circulation and, as has already been pointed out, the infant's hemoglobin concentration can be predicted arithmetically by postulating a maximum survival period for the donor's erythrocytes of twelve weeks. As the infant's total red cell count drops, the question will arise whether the infant should be re-transfused. In making this decision, one should be guided not only by the blood count, but also by the smear for reticulocytes and the differential agglutination tests. The appearance on the smear of a shower of reticulocytes is a sign of active regeneration—and in such cases, transfusions may be withheld even when the hemoglobin concentration is as low as 50 per cent. If the differential agglutination tests show no Rh-positive cells and there are no reticulocytes on the smear, a small supplementary transfusion of about 60 to 70 cc. of blood may be advisable when the hemoglobin concentration drops below 60 per cent.

An interesting observation is the presence of a high eosinophilia which persisted up to the sixth week of life. The coincidence between the period of the eosinophilia and the period of bone marrow aplasia supports the idea² that the apparent aplasia is due to the persistence in the fetal body of maternal Rh antibodies which destroy any new ery-

TABLE III

<i>Blood of</i>	<i>Group</i>	<i>M-N Type</i>	<i>Rh-Hr Type</i>
Father	O	MN	Rh ₁ rh
Mother	O	M	rh
Older Brother	O	M	Rh ₁ rh
Patient	O	MN	Rh ₁ rh

throcytes as quickly as they are released from the bone marrow. That is, the eosinophilia probably reflects the continued presence of an antigen-antibody reaction in the infant's body.*

CASE 2. The patient was a female infant born at the Adelphi Hospital on September 24, 1946. Shortly after birth jaundice was noted, and the possibility of erythroblastosis was considered despite the fact that the blood count was normal. The infant was the second child. The results of grouping and Rh-Hr tests on the family are shown in Table III. Tests for Rh antibodies in the mother's serum revealed the presence of anti-Rh₀ agglutinins of 50 units titer.

Since the presence of anti-Rh agglutinins (bivalent antibodies) of such high titer is usually associated with the syndrome of icterus gravis the patient was in imminent danger of developing kernicterus. An immediate exchange transfusion was carried out; 500 cc. of group O, type rh blood were injected and 450 cc. withdrawn. The procedure went very smoothly. Approximately 100 cc. of blood had run into the infant by the time the bleeding had started, and this initial advantage was maintained throughout the procedure. The total dosage of heparin was again 0.6 cc., administered in divided doses of 0.2 cc. each, the last being given at about the middle of the procedure. The heparin effect had been completely nullified by the time the procedure was completed so that it was not even necessary to ligate the blood vessels.

The infant's subsequent course was uneventful. Jaundice disappeared within twenty-four hours and thereafter the baby exhibited no further evidence of the disease.

The hematological findings before and after the transfusion are shown in Table IV. It will be seen that before transfusion the blood count was essentially normal and the smear showed only 2 nucleated red blood cells per 100 W.B.C. However, there were many polychromatic erythrocytes present and the icterus index was 45 units. On the day following the transfusion (fourth day of life) the hemoglobin concentration of the blood was 113 per cent and the blood smear showed no abnormalities, there being no polychromatic cells or nucleated red blood cells. Differential agglutination showed that a 90 per cent replacement had been effected. On the sixth day the hemoglobin concentration was found to be 95 per cent and differential agglutination showed that this drop

(Case II continued on page 217)

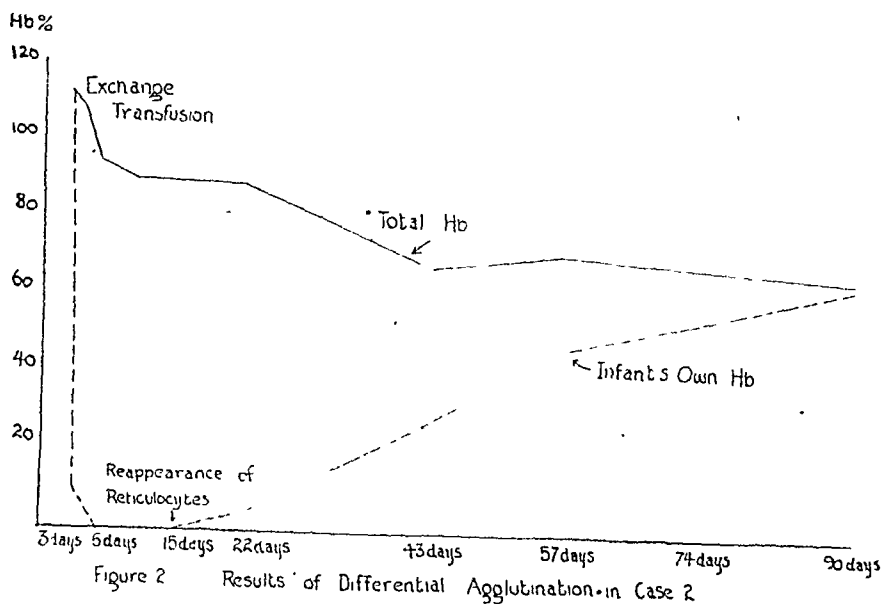
* The relatively continuous presence of an eosinophilia in cases of erythroblastosis while there is an antigen-antibody reaction going on has suggested to one of us (W.) a new line of investigation. As is well known, histamine is released during allergic reactions but the source of the histamine has never been satisfactorily explained. The idea that histamine may be derived from the eosinophilic granules deserves consideration for the following reasons: (1) There is a close correlation between the release of histamine and eosinophilia. (2) The histamine concentration of the blood is highest in the white blood cell layer. (3) The acidophilic staining reaction of the eosinophile granules could readily be explained by the presence of a base like histamine. Direct evidence supporting this theory has already been reported by Code.¹⁷

TABLE IV
RESULTS OF HEMATOLOGIC STUDIES IN CASE 2

	Time when tests were made									
	3rd day; before exchange transfusion	4th day	6th day	10th day	15th day	22nd day	43rd day	57th day	74th day	90th day
Hemoglobin per cent	117	113	95	90	90	90	70	75	75	72
RBC (mill./mm.)	5.5	—	43	4.3	4.7	4.3	3.51	3.69	—	—
WBC (mill./c mm.)	16,000	—	11,400	9,800	15,600	12,800	—	—	—	—
Neutrophils: segmented band	40	44	49	45	45	31	18	28	18	—
	4	5	5	2	3	2	1	1	1	—
Lymphocytes	45	39	30	46	42	56	70	58	71	—
Monocytes	7	8	13	3	8	7	7	6	3	—
Eosinophiles	2	3	3	3	3	3	4	7	4	—
Basophiles	1	0	0	1	0	1	0	0	0	—
Myelocytes	1	1	0	0	0	0	0	0	0	—
Nucl. RBC/100 WBC	2	none	none	none	none	none	0	0	0	—
Reticulocytes	3%	none	none	none	1/2 %	1/2 %	1/2 %	1 1/2 %	1%	1 1/2 %
Differential agglutination	100% Rh ₁	$\frac{1}{10}\text{Rh}_1 + \frac{9}{10}\text{rh}$	100% rh	100% rh	100% rh	$\frac{1}{20}\text{Rh}_1 + \frac{19}{20}\text{rh}$	$\frac{1}{2}\text{Rh}_1 + \frac{1}{2}\text{rh}$	$\frac{11}{12}\text{Rh}_1 + \frac{1}{12}\text{rh}$	—	99% Rh ₁

was due to the elimination (by hemolysis) of the remainder of the infant's own Rh-positive red cells. How severe the disease process might have been if the infant's blood had not been withdrawn can, of course, only be surmised. The complete and rapid destruction of the residual 10 per cent indicates that the process would almost surely have been severe. On the 15th day the hemoglobin concentration was still 90 per cent, and by this time reticulocytes reappeared on the blood smears, so that effective regeneration had already begun. From this time onward the blood count was maintained within safe limits as the production of the infant's own cells practically kept pace with the elimination of the donor's erythrocytes. The infant's red cells were once more demonstrable in the differential agglutination preparations as early as the twenty-second day of life.

The less impressive hematological findings in this case as compared with case 1 may be explained by the difference in the type of antibody produced by the mother. According to the evidence presented by Wiener,^{9, 15} univalent antibodies, such as were found in case 1, pass the placental barrier more readily than do the bivalent antibodies such as were found in this case. In typical cases, the univalent antibodies coat the fetal red cells and give rise to a gradually progressive hemolytic anemia. These antibodies are capable of traversing the placenta only during the last trimester of pregnancy, at which time, if they are of sufficiently high titer, they may give rise to stillbirths. If the child is born alive and has good hepatic function, jaundice will be minimal. If hepatic function is poor, jaundice and its accompanying toxicity will be present, laying the ground work for kernicterus to develop, should intravascular conglutination with capillary damage to the brain occur. Bivalent antibodies, on the other hand, apparently gain access to the circulation principally during parturition, and the infant at delivery often appears quite normal. When intravascular agglutination takes place, it usually occurs without warning so that an infant who appears to be thriving may die suddenly without developing anemia. We were fortunate in case 2 to be able to institute treatment before intravascular agglutination occurred. Not every case in which the maternal serum contains bivalent Rh antibodies is doomed to have kernicterus. The clumping of the red cells is a reversible process up to a certain point in vivo as well as in vitro, so that the flow of circulation tends to cause dispersion of the cells as quickly as the clumps form. This process of repeated agglutination and dispersion of the red cells damages them so that in such cases a rather abrupt drop in the hemoglobin is not an unusual finding. This mechanism may explain the sudden drop in hemoglobin that occurred in case 2. Differential agglutination proved the drop to be due to the elimination of the infant's own Rh-positive cells



rather than the donor's cells because thereafter all of the circulating erythrocytes were type rh.

Of interest is the relatively short period of apparent bone marrow aplasia* in this case as contrasted to that of case 1 (cf. Fig. 2). This is understandable on the hypothesis that the agglutinins enter the body of the infant mainly during labor and were largely removed by the exchange transfusion. On the other hand, univalent antibodies pass through the placenta continuously during the latter part of pregnancy and accumulate in the fetal body in quantities large enough not only to coat the erythrocytes, but also to permeate the blood serum and tissue fluids. Therefore, in such cases only a small portion of the antibodies are removed by the exchange transfusion.

DISCUSSION

While this paper was in preparation a communication by Wallerstein¹⁶ appeared, in which he described the results of twelve cases treated by substitution transfusion. In ten of these cases the blood was withdrawn from the sagittal sinus, while the radial artery was used in only two cases. Nine of the twelve cases treated recovered. Of the three cases that died, one had been given heparin to facilitate the bleeding from the radial artery and at autopsy a tentorial laceration, with marked

* Since the apparent aplasia is really due to hemolysis of the infant's red cells by the Rh antibodies remaining in its body, as quickly as the cells are released from the bone marrow, this period is perhaps better named "the phase of ineffectual regeneration."

hemorrhage was found. Wallerstein concludes that since silent intracranial hemorrhage is relatively common in the newborn infant, heparin is a dangerous drug to use.

As a matter of fact, our experience has proved that heparin administered according to our dosage schedule is perfectly innocuous. To date, we ourselves have treated nine infants, and three additional infants were treated by three other workers following our directions. All but one of these twelve infants made a spectacular recovery, although five of them were desperately ill when treatment was instituted. The infant who died showed, at post-mortem, kernicterus with liver damage, but no evidence of any hemorrhage. Incidentally, this patient was given 100 cc. more blood than was withdrawn. Had our modified technique been used, in which one half the donor's plasma is removed and replaced with saline and the amount of blood injected is not allowed to exceed by more than 50 cc. the quantity of blood withdrawn, we believe that the outcome even in this case would have been favorable. In addition, P. Vogel informs us that he has performed five exchange transfusions with the aid of heparin, all with favorable results. It therefore seems obvious to us that in the case Wallerstein mentions the death was due not to the heparin but rather to the hemorrhage secondary to the tentorial tear. After all, infants who have not received heparin frequently die as a result of intracranial hemorrhage caused by tentorial tears.

SUMMARY

Two cases of erythroblastosis are described in detail, which were treated by the method of exchange transfusion. In one case, the maternal serum contained univalent Rh antibodies (glutinins) and the other case bivalent Rh antibodies (agglutinins). These cases illustrate the spectacular effect of exchange transfusion in treating erythroblastosis. By the method of differential agglutination it was demonstrated that in the infant whose mother had the univalent antibodies the infant had a period of apparent aplasia persisting up to the thirty fourth day, while in the infant whose mother had bivalent antibodies the period of aplasia terminated on the fifteenth day. This supplies further evidence to support the thesis that the different clinical manifestations of erythroblastosis are due to differences in the quality of the maternal Rh antibodies.

The method of exchange transfusion described is simple. It entails

the use of heparin, the injection of the donor's blood into the saphenous vein at the ankle, and the withdrawal of the infant's blood through the radial artery at the wrist. Of a total of seventeen infants treated by this technique, many of whom were critically ill, all but one made a prompt and lasting recovery. This demonstrates the effectiveness as well as the safety of the procedure.

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EIGHTY YEARS OF PUBLIC HEALTH IN NEW YORK CITY *

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Commissioner of Health, City of New York

SIR Ronald Ross once wrote that most people take the great medical discoveries for granted because they have no conception of the vast number of workers and the years of effort that were necessary to make those discoveries possible. The present advanced state of public health is not due to any one person. It exists today because many men and women dreamed and planned and labored. They worked ceaselessly until their theories were translated into actualities.

This year marks the eightieth anniversary of the founding of the Department of Health of the City of New York. However, that doesn't mean that it is only eighty years that the City administration has been interested in the health of the people. Soon after the Revolutionary War, attention was given to the health problems of the day. These consisted, for the most part, of epidemics of yellow fever that reached New York and Boston. In 1798 the inhabitants of this City were panic-stricken by the rapid spread of this dread disease, and they fled as far north as Greenwich Village hoping to outdistance it. At that time New York City had a population of 60,000. Two-thirds of the residents were stricken with yellow fever, and of these 1,500 died. Sixteen of the forty physicians practicing lost their lives in that one epidemic. Up to that time the City had no power to make health regulations, but the need for such power in order to meet emergencies was recognized and in 1799 the State Legislature granted the City authority to pass its own health laws.

The first written evidence of the existence of health administration in New York City is the report made in 1806 by John Pintard who was City Inspector during the first decade of the nineteenth century. The exact date when he took office is uncertain but he was appointed March 26, 1804. The report was addressed to DeWitt Clinton who was

* Address delivered at The New York Academy of Medicine November 8, 1946 before the Section of Historical and Cultural Medicine and the New York Society for Medical History.

Mayor of the City and President of its Board of Health.

Pintard recorded that six hundred persons had died of yellow fever in 1805. In that year the population of New York City was 75,000. This made the death rate from yellow fever 8 per 1,000 of population.

The City Inspectors who served in the early part of the century were keenly aware of the importance of accurate vital statistics. In his report of 1810 Inspector Pintard pointed out that the statistics of the day could not be depended on in every instance because of incomplete and, in some cases, erroneous reporting. He felt that accurate records would make "bills of mortality" of incalculable benefit not only to physicians but to all interested in the health and welfare of the people.

City Inspector Dunnell in 1838 also called attention to the need of reliable statistics. He was the first inspector to recommend the maintenance of a registry of births and marriages. Cornelius B. Archer, City Inspector in 1845 and 1846, succeeded in securing the enactment of a law providing such registration. It was not very effective because there was no penalty for failure to report. Archer also urged improved sewerage, and the establishment of a hospital for pestilential and epidemic diseases. His successor was A. W. White who labored unceasingly to have the City's vital statistics accurate. White was also very much interested in the nomenclature of disease. He recommended that a complete sanitary survey be kept in the office of the City Inspector. He was the first inspector to make such a survey. In his report of 1850 he called attention to the salutary effect the introduction of Croton water six years earlier had had on the health of the people.

Apparently convinced of the value of the recommendations of his predecessors regarding vital statistics and analyses of sanitary conditions, Thomas K. Downing, City Inspector from 1852 through 1854, established two bureaus, that of Sanitary Inspection and that of Registry and Statistics. These bureaus have remained as part of the organization of the Health Department.

Inspector Morton who served from 1855 through 1857 was interested chiefly in sanitary matters. Incidentally he kept very careful records, and the City's vital statistics of those years are quite dependable. He was a pioneer in recommending greater playground facilities for children and the construction of experimental dwellings. Thus the recognition that proper housing and adequate recreational facilities are intimately related to public health is not as recent as many people think.

Inspector Delevan in 1858 complained of crowded, ill-ventilated railroad cars. Time hasn't brought any radical change in this matter because similar complaints can be heard today.

Dr. Stephen Smith in his book, "The City That Was," referred to the City Inspectors as incompetent and corrupt. Some of them undoubtedly were, but it would be unfair to brand all of them as such. Many, as those mentioned above, were honest, intelligent and capable men working under great handicaps. They succeeded in instituting measures which are recognized today as sound public health practice.

You may wonder why mention is made of a Board of Health long before the establishment of the Metropolitan Board in 1866. Boards of Health were temporary committees called by the State Legislature to deal with specific emergencies such as yellow fever and cholera epidemics. A State law in 1807 empowered the Common Council of the City to appoint a Board of Health consisting of the Mayor, the Recorder, the Commissioners of the State Quarantine Office and five other members. This Board recommended measures to the Common Council for dealing with health emergencies. Very often the measures were much more costly than they were effective. Once when a cholera outbreak threatened, it was suggested to Mayor Fernando Wood that he call a meeting of the Board of Health. He replied that the Board was more to be feared than the pestilence.

It is important that we recall something about the City as we trace its public health development. In the first quarter of the last century the northern boundary of the built-up portion of the City was Canal Street. The City appears to have been reasonably clean and tidy. On the whole, housing was favorable, and gardens and orchards were common. There were no tenements. Water was obtained from private wells. Some purchased it from a company that piped it through wooden conduits laid beneath the streets, while others bought it a bucketful at a time from peddlers driving a horse-drawn cart resembling a modern street sprinkler. There were outdoor privies. Water closets didn't appear until after the introduction of Croton water in 1842. The general death rate was about 25 per 1,000 population, and the infant mortality ranged between 120 and 140 per 1,000 live births. It must be remembered; however, that the statistics weren't entirely accurate at that time. New York City was relatively free of serious epidemics during the first quarter of the nineteenth century, although yellow fever which

had devastated the City in 1798 reappeared in 1805 and 1822.

In the second quarter of the century conditions changed rapidly. The City grew by leaps and bounds. The invention of the steam engine ushered in the industrial revolution. In 1845 a severe famine in Ireland caused thousands to emigrate to this country, and in 1848 the great social revolution which swept through Europe brought additional thousands of immigrants to our doors. The housing situation became acute. Poorly constructed houses were erected and cellars became living quarters. In the struggle for survival workers, especially the unskilled, were forced to work for less and less. The standard of living dropped sharply, and the panic of 1837 accelerated this drop. The City became increasingly insanitary. Three cholera epidemics, one in 1832, another in 1834 and the third in 1849, took nearly 10,000 lives. By 1850 the infant mortality rate had risen to 180 per 1,000 live births.

It was late in this second quarter of the century that the campaign for pure milk began, and surprising as it may seem this was incidental to a temperance crusade. The man who was responsible for calling attention to the need for reform in the milk industry was a prohibitionist named Robert Hartley. He found that the mash which remained after the whiskey had been made was sold to dairymen for feed. He visited barns and stables to see what effect this diet had on the cows. He found both the cows and the places where they were housed in a deplorable condition. The cows were undernourished, many of them diseased, and the places where they were kept were unbelievably filthy. In 1848 the Academy of Medicine which was then only a year old appointed a committee to study the milk situation. Despite its efforts and those of Frank Leslie, the publisher, very little was accomplished. More than sixty years were to pass before the people living in New York City had a safe and wholesome milk supply.

It was during this same second quarter of the nineteenth century that Edwin Chadwick, a lawyer living in England, put forth the thesis that the care of the health of the population was a function of good government. He had been influenced by Jeremy Bentham who, earlier in the century, had said, "All factors which influence the health of a community must be the concern of a legislature." In 1842 Chadwick made his famous "Report on the Sanitary Condition of the Labouring Population of Great Britain," which stimulated much interest. Six years later, a general Board of Health was created in England. Chadwick

was assisted by Southwood Smith, a physician. This partnership of law and medicine in behalf of public health was repeated in New York City a quarter of a century later when Dorman B. Eaton, a lawyer, and Stephen Smith, a physician, drafted the bill creating a Metropolitan Board of Health. In the opinion of as great an authority as the late Dr. William H. Welch, Eaton's contribution to health administration in this country ranks with that of Chadwick in England.

The third quarter of the nineteenth century brought with it a continuance of the rapid growth of the City with an accompanying increase in insanitary conditions. There was great dissatisfaction concerning the filthy condition of the streets and the general inefficiency of the health administration. It was a common practice to throw garbage and papers in the street, and these remained there for long periods of time. Dr. William Guilfooy who for many years was Registrar of Records in the New York City Department of Health was born in 1859 in the lower west side not far from the Washington Market. He told how youngsters in his day would earn a few nickels by standing at Broadway near City Hall with a broom, and when a lady or a gentleman wanted to cross the street, they would sweep a path through the muck.

In the early 60's, there were nearly two hundred slaughter houses in the City, many of them in thickly populated sections. Cattle, hogs and sheep were constantly driven through the streets, which were soon covered with their excreta. Blood and refuse from the slaughter houses added to the filth. Manure heaps from the numerous stables and farms were ever-present.

These facts were included in the report prepared by the Citizens' Committee of which Peter Cooper was president. The object of this Committee was to seek reform in all branches of municipal government. The bill for the establishment of a Health Department and a Board of Health in New York City was first drafted by Dr. Smith, Chairman of the Committee's Council of Hygiene and Public Health. It was put into final form by Mr. Eaton, the Committee's Counsel. It was passed by the Legislature in 1866.

Even prior to this time, namely in 1858, the Senate appointed a "Select Committee" to examine health administration in the city and to recommend legislation necessary to increase its efficiency. Apparently the report of this committee was not strong enough to bring about the needed change in health administration, for nothing was done. It was

for this reason that the Citizens' Committee was formed. Then, as now, intelligent citizens banded together to fight for essential reforms.

As organized under the Act of 1866, New York City's health administration was placed in the hands of a Board of Health for the metropolitan sanitary district of the State of New York. This district comprised the counties of New York, Kings, Westchester and Richmond, and the towns of Newtown, Flushing and Jamaica in the county of Queens. In 1870 the Board's jurisdiction was limited to the old City which included only the Boroughs of Manhattan and the Bronx. The first Board consisted of a president, appointed by the Mayor, four physicians who were sanitary commissioners, the health officer of the Port of New York and four police commissioners. A physician was appointed as sanitary superintendent in charge of the Bureau of Sanitary Inspection, and another physician was made Registrar of Vital Statistics. Mr. Eaton was named counsel. The Board of Health was empowered to make laws governing health and sanitation and to sit in judgment on violators. It is to the credit of the men who drafted the bill establishing the Board of Health that they recognized the need for giving it such broad and unprecedented powers.

During the first year of the Board's existence, there was a severe cholera epidemic in the City. Two army barracks were converted into hospitals and were placed under the supervision of Dr. Stephen Smith. Dr. Smith was also directed to organize a corps of physicians, some of whom would work in the dispensaries and others who would make house-to-house visits. Certain buildings were selected which could be used as temporary quarters for those families that would be removed from houses in which there were cases of cholera. The report of 1866 goes into considerable detail concerning the disinfectants utilized. Those most frequently employed were sulphate of iron, chloride of lime and soda, permanganate of potash, carbolic acid, and sulphur for fumigation.

It must be remembered that when the Health Department was formed, the germ theory of disease was still unknown and the chief function of the Department was the elimination of nuisances and the improvement of sanitation. Epidemics were fought by trying to neutralize the noxious gases in the atmosphere, gases which were the result of putrefying animal and vegetable matter.

It was the sanitary superintendent, Dr. Edward B. Dalton, who or-

ganized an ambulance service for Bellevue Hospital in 1869. Dr. Dalton, a colonel in the Civil War, had had considerable experience with the transportation of wounded soldiers. The removal of cases of smallpox had formerly been under the jurisdiction of the metropolitan police, but was now transferred to the Board of Health. Thus, the first satisfactory hospital ambulance service in New York City originated with the Health Department.

According to its second annual report, the Board of Health was concerned with the great prevalence of venereal diseases in New York City. It recommended that all hospitals and dispensaries receiving financial assistance from the State be obliged to treat venereal diseases.

In 1868 and 1869, important activities of the Department of Health included: Fixing a standard for illuminating oil; installing public drinking fountains in various parts of the city; erecting a public comfort station at Astor Place; taking action against the escape of offensive odors from lime and shellburning establishments; making a city-wide survey of tenement houses; and providing for the destruction of dogs believed to be rabid.

Although not established as a Bureau until many years later, the beginning of the Food and Drug Division was made in 1868 with the appointment of Professor Charles F. Chandler as chemist to the Department. Chandler's analyses showed that a fraud was being perpetrated on the public by the systematic dilution of milk with water. He estimated that the dilution was costing the people of this City about \$12,000 a day. In 1869 he turned his attention to the cosmetics that were being sold in the city. This was in response to a resolution of the Board that he examine hair tonics, washes and restoratives to find out if they contained injurious matter. His analyses revealed the presence of considerable quantities of lead. The next year he continued his examination of cosmetics and said, "Periodical publication of poisonous cosmetics would undoubtedly diminish the evil to a great extent."

By 1870, two more bureaus had been added to the Health Department—the Bureau of Street Cleaning and the Bureau of Sanitary Permits. In that year also, 200 cases of yellow fever occurred on Governor's Island, the first appearance of this disease in New York City since 1822. Dr. J. C. Nott, a physician practicing in this city, leaned strongly towards the germ theory of disease in discussing the nature and spread of yellow fever. He even suggested that it might be com-

municated by insects.

In 1871 there were reported in New York City 3,084 cases of smallpox with 805 deaths from that disease. In the same period, there were 146 cases of typhus fever. During that year, 100,000 persons were vaccinated.

The subject of infant mortality wasn't given much consideration until 1874 by which date the City's rate had climbed to approximately 240 per 1,000 live births. Then there was clamor for some action that would halt the steady rise. A leaflet on infant care was printed in simple language and distributed to tenement house dwellers. In the same year the Board of Health was confronted with the smoke nuisance created by the New Haven, Harlem and Hudson River railroads above 42nd Street. The Board condemned this as detrimental to public health and appointed a committee to confer with the superintendents of the railroad who, the report states, were most cooperative and did what they could to reduce the smoke to a minimum.

Smallpox was a serious problem in 1874 and the Legislature transferred the smallpox hospital from the jurisdiction of the Commissioners of Charities and Corrections to the Health Department, changing its name to Riverside Hospital. During the winter of 1874 and 1875, two thousand cases of smallpox were reported. Of the 1,025 which were allowed to be treated at home, 50 per cent died. In October, 1874 a corps of vaccinators was organized, and more than 126,000 individuals were vaccinated. Over \$1,200 worth of vaccine was sold to physicians, druggists and health departments outside of the City. Some 24,000 quill points were distributed free of charge to charitable institutions. At the time that the corps was organized, a bill was passed by the Legislature providing for the establishment of a laboratory for the preparation of vaccine virus and for the sale of any surplus. The money received constituted a fund which was used by the Board of Health to promote vaccination.

Diphtheria was prevalent in 1874. The Board of Health prepared and distributed leaflets describing what was then known about the disease. An intensive study of diphtheria was made with special emphasis on its micropathology.

In 1875 following the death of four individuals from hydrophobia, Dr. Charles R. Russell, sanitary inspector, recommended that dogs that bit human beings should not be destroyed immediately but should

be kept under close surveillance until the suspicion of rabies was allayed or confirmed. He suggested further that "valuable and esteemed animals" which may have been in contact with rabid dogs should be kept under observation under suitable conditions for at least six months. Since there was no rabies vaccine in those days, nothing could be done for the person bitten beyond cauterizing the wound.

Because the infant death rate rose sharply during the summer months, a "summer corps" of physicians was organized in 1876 to visit every tenement house; to prescribe for the sick infants; advise on hygienic measures; and distribute leaflets on infant care. In 1879 the State Legislature passed a law requiring the Board of Estimate to appropriate each year the sum of \$10,000. This was known as "The Tenement House Fund," and enabled the Health Department to employ this special corps of physicians. This summer corps was in fact the beginning of the Division of Child Hygiene which was to be formally organized as a bureau some thirty years later.

In those days Health Department physicians, who were called sanitary inspectors, had many and varied duties. They investigated tenement houses for defective plumbing, drainage and ventilation; visited cases of smallpox, typhus fever and other contagious diseases; performed vaccinations; and made sanitary surveys. Many of them rose to be leaders in the field of public health.

The first important step in getting a safe milk supply for New York City was the work of Professor Chandler who described the common practice of watering milk. The next step was taken by Ernest J. Lederle, who in 1892 was Acting Chemist.* Lederle seized the milk taken from diseased cows and had it inoculated into guinea pigs. The guinea pigs developed tuberculosis from which they eventually died. This demonstration made a great impression on all public health workers, and convinced any who might still have doubted, of the need for a safe and wholesome milk supply.

In 1896 the Sanitary Code was amended to require a permit from the Board of Health in order to sell milk in this city. Such permits are now recognized as the indispensable basis for the administrative control of a city's milk supply. Six years later orders were issued to a creamery outside city limits to discontinue the practice of removing

* Dr Lederle became Health Commissioner ten years later, serving from 1902 to 1904. He was reappointed in 1910 and remained in that position until 1914.

cream from milk and adding coloring matter and formaldehyde to it before offering it for sale in New York City. The creamery refused to comply stating that the Department had no jurisdiction outside of the city. The Board of Health called a public hearing at which the milk company was asked to show cause why its permit to sell milk in this city should not be revoked. Following this hearing at which the milk inspectors' report was confirmed, the permit was revoked and the company driven out of business in New York City. After that the authority of the Board of Health in safeguarding milk sold in this city, whether it related to a practice inside or outside the city limits, was firmly established.

Dr. Roger S. Tracy who was Deputy Registrar in 1893, divided the city into sanitary districts when computing his statistics. In this way he was able to secure statistical information regarding health and disease among groups of people of like race and nationality living under similar conditions. This was the forerunner of district health administration.

Until 1880, it was the practice of small towns north of New York City to send their cases of smallpox across the Harlem River into the City. After being apprehended by our Health Department, the patients would be placed in the Riverside Hospital on Blackwell's Island. When the Board of Health realized that the City was being imposed upon in this way, the practice was stopped and Westchester was forced to build a small shack near the East River for the accommodation of its smallpox cases. One of the first persons to be hospitalized in the Westchester shack was a Negro, and when the indignant citizens of the community discovered that he was being "harbored" in their midst, they burned the shack and forced the caretaker and his patient into a boat setting them adrift in the river. These two found refuge on North Brother Island where they took possession of an unoccupied house. This was the beginning of the use of North Brother Island for the housing of patients with contagious diseases. Some years later, a building was erected and all smallpox cases in the city were transferred to it.

In the spring of 1885, a hospital for diphtheria cases was built at the foot of East 16th Street and named for Dr. Willard Parker, Vice-President of the first Metropolitan Board of Health and a leader in public health. A few years later, the City of Brooklyn, having decided to take care of its own cases of contagious disease, purchased property

north of Kings County Hospital for buildings to be used for that purpose.

The discoveries of Pasteur and Koch greatly changed methods of public health administration. Through the work of these scientists and their pupils the true sources of communicable diseases were revealed. No longer was it believed that disease was caused by germs in the atmosphere. Drs. Biggs, Prudden and Loomis, consulting pathologists to the Health Department, were practically the first health authorities to recognize the advent of a new era in medicine. Their recognition was evidenced in 1887 by their report to the Board of Health recommending that tuberculosis be officially declared a communicable disease, and be made reportable. A bulletin of information on tuberculosis was prepared and distributed in the tenement house districts. However, it was not until 1894 that the Board of Health finally accepted the recommendation that tuberculosis be made "a notifiable disease." It was due to Dr. Hermann Biggs' untiring efforts that this essential act in the control of tuberculosis was adopted.

It was in 1892 that the first municipal bacteriological diagnostic laboratory in the world was established by the New York City Department of Health. This also was due to the persistence of Dr. Biggs who for years had asked for the establishment of a division of bacteriology. In that year there was an epidemic of cholera in Hamburg and the danger of its spread to New York was recognized by all. When the members of the Board of Estimate read in the newspapers that five steamships from Hamburg were being detained at Quarantine because of cases of cholera aboard, and that five deaths from that disease had occurred on one of them, they were almost panic-stricken. They gave an attentive ear to any plan for avoiding the threatened pestilence. In that mood they withdrew their opposition towards a laboratory and voted funds for its establishment. Thus in September, 1892 an emergency laboratory for the diagnosis of suspected cases of cholera was opened on the third floor of a building at 42 Bleeker Street. Dr. Hermann M. Biggs was placed in charge and given the title, "Chief of the Division of Pathology, Bacteriology and Disinfection." Similar emergency laboratories had been set up in Hamburg, Bremen, Berlin and London but these were all disbanded after the cholera emergency had passed.

Under the able guidance of Dr. Biggs, the Health Department's laboratory was continued and expanded to become an important part

of the Department's services. Soon after it was opened, Dr. Biggs stated that "the laboratory was to determine the differential diagnosis between follicular tonsillitis and diphtheria; to make scientific investigation in regard to the organisms of cholera, yellow fever, anthrax, etc.; to estimate the number of bacteria in Croton water; to make bacteriological examination of milk, meat and other foods; and to determine the value of different disinfectants."

In April, 1893, Dr. Biggs brought Dr. William H. Park into the laboratory and assigned to him the problem of working out a practical method of aiding physicians in the diagnosis of diphtheria. Park devised the diagnostic outfits for making throat cultures, and with the help of Dr. Biggs organized the system whereby such outfits could be made available in conveniently located drug stores, and collected daily by messenger. In January, 1894, the laboratory began sputum examinations for tubercle bacilli. Sputum bottles were also made available at drug store stations. Among the laboratory procedures that were soon added were examinations for gonococci, for malaria and for typhoid (Widal reaction).

The establishment of this laboratory had an important influence on public health throughout the country, in fact, throughout the world. It was the first municipally owned diagnostic laboratory. It inaugurated procedures which were adopted by other health departments. It stimulated studies which resulted in a great improvement in the laboratory diagnosis of communicable diseases.

News of the good results reported by Von Behring on the use of the antitoxin in the treatment of diphtheria reached New York. Under the sponsorship of the New York Herald a fund was raised for the making of antitoxin and its distribution to diphtheria patients who were unable to pay for it. The fund was turned over to the Department of Health to be expended under the supervision of an advisory committee of eminent physicians including Dr. Biggs and Dr. Park. This was the beginning of New York City's antitoxin laboratory.

In 1895, legislation was enacted authorizing the Department of Health to produce, use and distribute diphtheria antitoxin and other antitoxins and to sell any surplus products. The proceeds from the sales were to be utilized for further studies in the production and use of the various antitoxins. These funds made possible the organization of the Research Division of the Bureau of Laboratories.

As a result of a Tenement House Act passed in 1895, the Health Department's Corps of Sanitary Inspectors was increased. In accordance with the provisions of the new law, two inspections were made of each tenement house in the City. The total number of inspections and reinspections during the year amounted to over 169,000 and resulted in the discovery of some 18,000 violations. At that time, there were nearly 41,500 tenement houses in the City. About 600 of them were ordered vacated by the Board of Health as unfit for human habitation. The order was rescinded in all but 68 cases because the owners of the houses immediately started to make the necessary repairs. The houses that were vacated were either beyond repair or their owners didn't take the Health Department's order seriously. Vigorous action against unfit tenements continued during the following years as the Board felt that "no branch of the sanitary work carried on by this Department is of greater importance to the public health." In 1901 the Tenement House Department was created and jurisdiction over all dwellings housing more than two families was transferred to it.

In 1898 the City of New York added to its territory by the incorporation of the City of Brooklyn and of several neighboring towns and villages. This act was technically called the Consolidation Act. The task then fell upon the Board of Health to acquaint the citizens of the newly added communities with the requirements of the Sanitary Code.

In the report of that year, drug control activities of the Department came to the fore, with particular attention to headache powders containing coal tar derivatives which were sold without prescription, and to "catarrh cures" containing cocaine. Many so-called remedies for drunkenness were found to contain as much alcohol as whiskey. Lead and morphine were among the dangerous ingredients found in other proprietaries. The recommendation was made that all of these deceptions, frauds and dangerous practices be suppressed by law.

Although the Division of Child Hygiene was not established until 1908, school medical inspections began with the appointment of 150 physicians in 1897. They were attached to the Division of Contagious Diseases, and were interested chiefly in the inspection of children who had been ill. In 1902 seventeen public health nurses were assigned to schools to assist the physicians. This was the first time in the history of the United States that nurses were assigned to this kind of work. In 1908, when the Division was finally established and placed under

the direction of Dr. S. Josephine Baker, a pioneer in infant welfare, its functions included: The control and supervision of midwives; the reduction of infant mortality; the supervision of foundlings boarded in private homes; the inspection and sanitary supervision of day nurseries; the inspection of institutions harboring dependent children; the medical inspection and examination of school children; the vaccination of school children; and the enforcement of that part of the Child Labor Law relating to the issuance of employment certificates. Infant milk stations, the forerunner of the child health stations, were set up in 1911. Except that the various functions of this bureau have been extended to meet changing conditions, the organization today is substantially the same as it was when the Division was organized almost forty years ago.

In 1902 and 1903, Drs. Park and Holt did important research on the relation between infant mortality and bacteria in milk. This study showed that cholera infantum, or as it was popularly called "summer diarrhea," was not caused by any specific pathogenic organism, but was due to large numbers of ordinarily harmless bacteria. The delicate mucosa of infants could not withstand their attack. Thus the importance of determining the numbers of bacteria in milk and other foods as well as the kinds of bacteria was clearly demonstrated. In spite of this report it was not until eight years later that the Board of Health added to the Sanitary Code a section requiring the pasteurization of milk offered for sale in New York City.

In 1906 the Health Department extended its milk inspection in a manner that was entirely new for a municipality. Inspectors were sent to farms in New York State and other states where milk was produced for sale in this city. In this way the Department had control of the milk from the time it was produced until it was delivered to the consumer. During the following year, a system of examining and keeping under surveillance all typhoid carriers in New York City was initiated.

Although the Health Department's venereal disease activities were not placed in a separate bureau until 1934, Dr. Hermann M. Biggs initiated a comprehensive anti-venereal disease program in 1912. This embraced: the reporting of syphilis and gonorrhea by private physicians, hospitals and clinics; offering the services of the Health Department's laboratory for Wassermann tests free of charge (gonococcus smears had long been a routine service); establishment of special clinics

for diagnosing and treating venereal diseases (darkfield examinations, and distribution of salvarsan); providing special hospital facilities where irresponsible patients could be forcibly detained until no longer infectious; an educational campaign against patent nostrums and quackery in the treatment of venereal diseases. This pioneer program has served as a model for all the work now carried on in this field throughout the United States.

Biggs looked upon venereal diseases from the point of view of a physician and a public health administrator. Venereal diseases are communicable diseases and it is the duty of the Health Department to use every available means to stamp them out. At Bellevue Hospital where Biggs had a medical service, he ordered routine Wassermann tests on all the patients in his wards. The Department of Health ran a paid newspaper advertisement warning against quacks. Signs bearing similar warnings were put up in the toilet rooms of saloons, restaurants and other public places. Soon after his appointment as Commissioner of Health of the State of New York, Biggs secured the enactment of legislation prohibiting advertising for treatment of venereal diseases throughout the State.

During Dr. Lederle's second term as Commissioner of Health (1910 to 1914) compulsory pasteurization of milk was introduced. The Department of Health was reorganized into eight bureaus: Bureau of General Administration, Bureau of Records, Sanitary Bureau, Bureau of Child Hygiene, Bureau of Infectious Diseases (later named Preventable Diseases), Bureau of Food and Drugs, Bureau of Hospitals and Bureau of Laboratories. In 1914 the Bureau of Health Education was established; in 1928, the Bureau of Nursing.

In 1934 the Bureau of Tuberculosis was set up as a separate unit, and this was followed the next year by the establishment of the Bureau of Social Hygiene. These diseases were considered to be of sufficient importance to warrant this change in administration. Up to that time, they had been under the jurisdiction of the Bureau of Preventable Diseases. In 1929 the contagious disease hospitals including institutions treating tuberculous patients were transferred to the Department of Hospitals. Although the District Health Center program as we know it today began late in Commissioner Shirley W. Wynne's administration, the first experimental health center was set up in New York City in 1915 under the direction of Commissioner S. S. Goldwater.

Approximately ten years ago, a plan was worked out whereby medical students were given practical training in the health centers. This was a logical development of the growing importance of preventive medicine in the medical school curriculum. No public health program can be completely successful without the active participation of all the physicians in the community. The Health Department is, therefore, eager to do all it can to acquaint both medical students and physicians with the public health problems and the means at hand for combating them.

Dr. Linsly R. Williams, who was Managing Director of the National Tuberculosis Association and Director of The New York Academy of Medicine, once said, "Public health is not hygiene or preventive medicine. It is a concept of the conditions of health of the community. Efforts to conserve the public health include both those which affect the health of the community as a whole, and those which seek to prevent any individual or group of persons from affecting adversely the health of others."* The last part of that statement is especially noteworthy today when the Health Department is making every effort to have food establishments operate in compliance with the provisions of the Sanitary Code. An ignorant or careless food handler is a definite health hazard. The owner is responsible for operating a food establishment in accordance with high sanitary standards, and the Health Department is determined that he be made to understand and fully meet that obligation.

In conclusion, it might be interesting to compare the health problems confronting us today with those faced by public health officers eighty years ago. Pestilence has been conquered. No longer are yellow fever, cholera, typhus and smallpox major health problems in New York City. The common communicable diseases that annually took the lives of thousands of children have been brought under control. The life expectancy at birth has increased from about 31 years in 1880 to over 65 now. Today increasing attention must be given to the diseases of later life. Public health officials, no less than physicians and social workers, must recognize their responsibility for making the added years gained through the saving of lives in the younger age groups, more healthful and more enjoyable. There must of course be no lessening of effort in the fight against communicable disease, but this

* "Role of Practitioners in Modern Public Health Work."—*Preventive Medicine and Public Health*, Thomas Nelson and Sons, New York—1928.

fight must be extended to include the diseases that are more prevalent among the elderly, namely, diabetes, cancer, diseases of the heart, blood vessels and kidneys.

We in the New York City Health Department feel certain that we will continue to have the wholehearted coöperation of the physicians practicing in this city. Were it not for their unselfish and untiring efforts throughout the years the story would have been quite different. Many of the great advances that have been made in improving the public health would probably never have been recorded. Special mention should be made of the many helpful suggestions given to the Department of Health by the Committee on Public Health Relations of The New York Academy of Medicine.

The Health Department has had a distinguished history. Not one or two but a host of outstanding men and women have been associated with it, and have produced methods and techniques that have become standard for health departments throughout the world. Those of us who are charged with the responsibility of protecting the public health today hope that we, like our predecessors, can overcome the obstacles of ignorance, superstition, prejudice and apathy; that we shall not falter in the job ahead, but that we may be enabled to carry on in the tradition of those who traveled the road before us.

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VICTOR ROBINSON

1886-1947

The conventional obituary of Victor Robinson will give the facts of his life, detail his literary contributions, and the titles awarded him by schools and universities. A personal note may not be amiss.

Close to a quarter century ago, because of a short historical note submitted to him as editor of *Medical Life*, Victor Robinson invited me to his offices on Mount Morris Park, West. Victor Robinson was an intense person, then. He remained an intense person for his life time. He radiated intensity of purpose and intensity of ideals. He became enthusiastic in the presence of one entering the portals of history of medicine. He welcomed each worker striving to unveil the influences of the past in medicine and culture upon the current scene. His own studies encompassed all the specialties of medicine and surgery; of dentistry; and of nursing. He knew the basic and the accessory facts regarding each group from earliest to modern times. The nature of Victor Robinson caused him to accept the offerings of each as if they were truly spectacular and earth-rocking in importance. He cherished each item as if it were the key to the entire historical structure.

Victor Robinson accumulated a store of information on the things that were and are not alone from books, but from experience. He made on the site investigations. He visited and revisited the cradles of our medical heritage. He relived the life of each of his hundreds of heroes. He seemed actually to have cast himself into the period, into the thinking of each epoch. Dr. Robinson surrounded himself with the memories of the person, with his home, his family, his politics. He came to know the streets he trod; yes, the very cobbler responsible for the sandals or the shoes or the boots each wore on his daily route from home to market place, to school. He suffered the tortures of each truthsayer bound to the fiery stake. He was elated with each honor heaped upon the chosen.

Victor Robinson had an astounding memory. He forgot nothing. He recalled minute things and dates and places and titles and books—especially books. He could discourse for hours on end at formal or informal lecture meetings on individuals or entire movements without one glance at a card or a paper. He conducted his classes without notes. His flow of language in speech and in writing was superb. His references covered the earth, and included each decade of man's residence here. His quotations were apt. How easy it is to say: Victor Robinson was a scholar.

Yes, Victor was a scholar, but he was no cloistered scholar. He knew the world about him. He felt the impress of each social change. He travelled to far distant places to gain his own impressions of these changes.

Perhaps the greatest measure of the man, for those outside his immediate family, was his capacity for friendship. He always found a moment to share with people. He never said an ill word of anyone. He accepted tasks from friends and from acquaintances. He read manuscripts for people he scarcely knew. He made helpful suggestions. He corrected errors. He softened harsh criticism. He gave freely of his time, his energies, and his knowledge. He accepted the teaching post and the professorship in medical history at Temple University in Philadelphia in 1929. He continued to teach, indeed increased the number of his courses although this required he awaken at five in the morning on Wednesday of each week of the academic year and travel to Philadelphia. He received no honorarium. He accepted no recompense other than the enthusiasms of his pupils. He taught medical students, and nursing pupils from the training schools of Philadelphia hospitals, denominational and otherwise. He conveyed his thoughts to eager groups. He felt lifted by their acceptance of his lecture and illustrative material.

Much regarding Victor Robinson re-

ained his very own. He never burdened friends with his difficulties or troubles. He never wore his heart on his sleeve. The days never seemed long enough for work and study. There were not enough evenings for discourse with friends. There never was enough time for gaiety. One can never forget those evenings at home at Mount Morris Park West of a decade ago. One was never certain what was to happen next. A singer from a stranded Italian opera company would give a concert right there; or an entire troupe would entertain. A musician lost in our land from Russia would find the piano. A scholar recently arrived from Holland would have a group in one corner of one of the rooms on one of the floors of the house. A painter with the ylang-ylang of the Parisian subway still clinging to his clothes would enthuse over the animated talk of an art student. A playwright, a public relations counsel, a book publisher, a highly rated specialist and a family physician, a down at the heel translator from the German—these would

rub shoulders at an evening at the Robinson's. Food and drink in abundance and talk in half a dozen languages at one time.

But best of all, one recalls Victor Robinson at his desk. Short, lean, he was at his desk ever piled high with reference books, dictionaries, biographies, galley proof, manuscript, editorial scissors, blue pencils. Victor with his glasses high on his forehead peering, ever peering at the word. He did so much, and had wished to do so much more. Two new books reached the stores about the time of his sixtieth birthday. His friends had submitted material for a Festschrift—some sixty articles had been contributed on medical-historical topics. The publication must wait now. It will be a memorial to Victor Robinson from his friends and co-workers in a field whose importance is ever increasing.

Many years ago, Victor Robinson wrote: "Interest in the History of Medicine has persisted, for it is the greatest of stories—the record of man's conflict with credulity."

HERMAN GOODMAN

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("Possession does not imply approval.")

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MAY 1947

THE ROLE OF THE ACADEMY IN THE
CITY AND THE NATION*

GEORGE BAEHR

President, The New York Academy of Medicine

THIS assembly of the Fellowship and the friends of The New York Academy of Medicine on the occasion of its one hundredth anniversary is gratifying evidence of your appreciation of the Academy's place in the life of the City and of the Nation. It would be regrettable if the high esteem in which the Academy is held were based today in too large a measure upon the things that meet the eye, our magnificent edifice on Fifth Avenue and 103rd Street with its impressive meeting halls and conference rooms, our great medical library, or even upon the high professional and scientific level of the Academy's Fellowship. These are delightful advantages to contemplate and enjoy. But we, Fellows of the Academy, should look upon them rather as symbols of the serious heritage of public responsibility which has been handed on to us by our predecessors over this century.

From small beginnings the Academy has grown through the years to be an indispensable instrument of American medicine. Although its name identifies it with a City, this has become more an indication of its location, for its educational and cultural influences extend through-

* Presidential Discourse delivered at the opening dinner meeting of the Centennial Celebration of The New York Academy of Medicine, March 6, 1947, at the Waldorf-Astoria Hotel, New York City.

out the Nation and even across the seas. Its influence in public health and in the advancement of scientific progress has contributed no small part to the present high standards of medicine in this country. The medical library, one of the largest and most useful in the world, and, in this country, exceeded only by that of the Surgeon General in Washington, now serves six times as many readers as his or, perhaps, any other medical library.

Over these one hundred years, the ideals, the toil and the savings of many distinguished Fellows have been contributed to keep alive the flame of inspiration of the Founders of the Academy through long periods of discouragement. It was their devotion to the public interest over the first three-fourths of a century which eventually won the confidence of the great philanthropic foundations, the Carnegie Corporation and the Rockefeller Foundation and persuaded these and other lay benefactors to come to our assistance in 1923 and help us reach the goal which we celebrate today.

As the fortieth president of the Academy, I shall, therefore, take advantage of this occasion to turn back the pages of history for a few moments in order to review the social and scientific forces at work in the world a century ago, which impelled its Founders to establish this institution. In endeavoring to reconstruct a picture of the times and the influences which motivated the Founders, I am assisted in no small measure by the material which has been assembled during the last two years by Dr. Philip Van Ingen in preparation for a volume on the History of The New York Academy of Medicine, which is to be published in this Centennial year. On behalf of the officers and the Council of the Academy, I gratefully acknowledge our indebtedness to Dr. Van Ingen for the arduous task which he has generously undertaken.

You will recall that the first half of the nineteenth century was characterized by extraordinarily rapid changes in the pattern of American life. Before the year 1800, our country had been a land of farms and hamlets for more than 150 years, and it was the ambition of Jefferson that we should continue to be forever "a nation of husbandmen." Before the end of his second term as President, Jefferson had already revised his views on industrialism under the pressure of changing exigencies. The Embargo of 1807 was followed by a succession of events, the British blockade during the War of 1812, and the subsequent protective tariff, which stimulated industrial undertakings along the Atlan-

tic Coast and greatly accelerated the growth of cities.

The rapidly changing order of the American scene is revealed by the fact that the number of persons engaged in manufactures, and also the number of city dwellers, increased 127 per cent in the twenty years between 1820 and 1840. In 1820, according to Schlesinger, only 5 per cent of the people of this country lived in communities of eight thousand or over; by 1840 the percentage had almost doubled despite the fact that the great drive to the West was helping to preserve the preponderance of agriculture. This wide dispersal of rural populations made conditions throughout the country unfavorable for any close association of physicians, and under this handicap the primitive medical practice of the time, with some notable exceptions such as Mac Dowell, Beaumont and Morton, remained a reflection of the vapid theorizing of the eighteenth century.

In contrast, the rapidly expanding business communities enjoyed the vital advantage of compactness and unity. The new economic life stimulated the establishment of new institutions not only for banking and business but also for general education and medicine. In the growing cities, some of the physicians and surgeons had derived part of their learning and inspiration from the great medical centers of Europe and the British Isles, under such medical pioneers as Louis, Laennec, Dupuytren and Velpeau in France, and Graves, Stokes, Bright, Addison, Hodgkin and Sir Astley Cooper in England, Scotland and Ireland. It is therefore comprehensible that increasing numbers of physicians followed their ambitious lay friends during the early part of the century and forsook rural life for the greater financial and cultural rewards to be found in the rapidly developing urban areas.

These turbulent times witnessed the flowering of American literature, the struggle for public schools, the beginning of the movement for woman's rights and other important humanitarian crusades. The growing intellectual demands of the country are reflected by the fact that in the brief span of twenty years between 1820 and 1840, 87 private colleges and 15 state universities were founded. In the year 1800, there were as yet only 5 good medical schools in the entire country, two of them in New York City. Although the number increased rapidly by 1847, inferior or irregular medical schools and medical cults increased disproportionately during this period. Improvement in the general educational level of physicians was further retarded by the fact that the

issuance of a license to practice medicine was the privilege of medical schools. Many were hardly more than finishing schools designed to complete a medical apprenticeship begun under a preceptor. As a result, medical cults and quackery flourished bountifully. In view of the many reform movements of the times, it is, therefore, not surprising that medical leaders in 1846-47 should also have felt the need for decisive action to clear away the debris of intellectual disorder within their ranks and prepare the way for the promising scientific developments which already loomed on the horizon but were not yet clearly visible.

By 1847, American surgeons had become noted for their skill, and there were already promising evidence of Yankee ingenuity in the medical field. Beaumont had made his studies on human gastric physiology in 1825 and ether had been introduced for general anesthesia in Boston in 1846. As the Founders of the Academy perhaps did not realize, 1847 was the momentous year of the publication of Helmholtz' work on the Conservation of Energy wherein was established the First Law of Thermodynamics. This principle, as subsequently extended by the great American, Willard Gibbs, was to make biology and medicine a branch of chemistry and physics. Darwin was as yet only laying the groundwork for the *Origin of Species* (1859) and Pasteur was beginning to advance slowly and laboriously through crystallography and fermentation to his momentous discoveries in bacteriology, immunology and sanitation.

The first half of the nineteenth century was also the time when Edwin Chadwick, administrator of the Poor Laws of Great Britain, was "making the welkin ring" with his insistent demands that steps be taken by government to prevent the recurring epidemics of disease. It was evident to him that poverty could in large part be prevented by reducing disease and mortality. By 1840, he had finally stimulated the public authorities of Great Britain to action and in 1848, the year after the founding of our Academy, he became the head of the first Board of Health. Chadwick's greatest contribution was his enunciation of the principle that public health measures for the control of disease, unlike the Poor Laws, must be applied for the benefit of all the people. I have no doubt that the great voice of Edwin Chadwick was heard across the seas, and that it played its part in arousing the obvious concern of the young Academy with problems of public health and, more especially, the control of epidemic diseases even though the causes were

unknown at that time and the methods of their transmission were still the subject of bitter controversy.

The same forces and in fact some of the same medical leaders who directed the founding of the Academy were responsible for the almost simultaneous organization of the American Medical Association. In both instances the compelling motives were the need for higher standards of medical education and licensure and for the elimination of charlatanism by the adoption of a code of medical ethics and by public education. The first preliminary meeting for the establishment of a national medical association was held in this City in 1846 at the New York University Medical College under the chairmanship of Dr. Edward Delafield. It was resolved to hold a convention in Philadelphia the following year. In that convention which established the American Medical Association, the newly organized New York Academy of Medicine was represented by the largest delegation, 16 members out of a total of 78 delegates. Our delegation included such men as Delafield, Stearns, Mott, and the Academy's energetic secretary, Campbell Stewart. Not only did the primary incentive for the organization of the American Medical Association come from the State of New York, but at that first official assembly of the Association in Philadelphia in April 1847, the influence of the Academy's 16 representatives was as great as that of the delegates from any of the State Medical Societies or medical colleges.

The founding of the Academy a hundred years ago was inspired by the need for an independent institution in which physicians of high professional standards could find opportunities for mutual improvement and for public service. On November 18, 1846, a sumptuous dinner was held in an elegant saloon at 579 Broadway under the chairmanship of the venerable Dr. Delafield to celebrate the fourth anniversary of the Society for the Relief of the Widows and Orphans of Medical Men. The Society is still active today and its present officers are here tonight to join us in our Centennial celebration. Toward the end of that dinner in the Fall of 1846, being well refreshed with excellent food and wine, the famous surgeon, Dr. Valentine Mott, President of the New York University Medical College, rose and proposed a toast to the older College of Physicians and Surgeons. Not to be outdone, the President of the College of Physicians and Surgeons, Dr. Alexander M. Stevens, rose to return the compliment. Warming up to the occasion, he ended a stirring

address by urging the establishment of a medical hall with ample meeting rooms and a library which would be independent of the medical schools and hospitals and would bring together eminent members of the profession for the purpose of improving the deplorable standards of medical education and medical practice of the time.

After the dinner, forty or more physicians remained behind to discuss these exciting proposals. Dr. John Stearns was voted into the chair, and before this rump meeting adjourned, a committee consisting of Dr. Mott, Dr. Stevens and Dr. Isaac Wood was instructed to call a general meeting of the profession at the Lyceum of Natural History at 561 Broadway "to establish an Academy of Medicine and Surgery and to provide a permanent place for its meetings." Within a few weeks, 185 physicians had enrolled as Founders and at the first formal meeting at the Lyceum on January 13, 1847, the Constitution and By-Laws were adopted, the name New York Academy of Medicine was approved and Dr. John Stearns was elected as the first president. In his inaugural address at the first Stated Meeting of the Academy on February 3rd, Dr. Stearns stated that the purposes of the new institution were "to elevate the standards of medical education, to exclude from our ranks all ignorant pretenders, to enlighten the public mind on the subject of medicine and its collateral branches of science and to take all necessary means to promote the honor, the dignity, the respectability and the usefulness of the medical profession."

In contrast with the high and noble spirit of the enthusiastic Founders, the first home of the Academy was only a rented room over a coal yard at 175 Wooster Street. In spite of an imposing name, Convention Hall, it had space neither for a library nor for the monthly Stated Meetings of the Fellowship. So, during the first 28 years large meetings of the Fellows were held at first at Lyceum Hall on Broadway, for 18 years (1850-1868) in the small Chapel of New York University on Washington Square, and, toward the end of that period, in the lower lecture room of the College of Physicians and Surgeons at 23rd Street and Fourth Avenue.

The medical library, one of the original proposals of Dr. Stevens, was not forgotten. In fact, it was established ceremoniously at the first meeting of the Academy on January 13, 1847 when Dr. Isaac Wood formally presented a copy of Paine's Commentaries in three volumes as the first contribution to the new library. From this small acorn grew

the great oak, but not without weathering many a storm.

At first, the books were kept in the home of the Fellow who had been elected librarian, Dr. Thomas Cock. After Dr. Cock had patiently given the library shelter for 11 years, it was moved for a time to a room adjacent to the library of New York University. But during the Civil War (1865) when the finances of the Academy had sunk almost to insolvency, an increase in the room rent from \$7.50 to \$12 a month promptly drove the library back to the home of the new librarian, Dr. John Henry Hinton. It was not until 1875 that Fellows and their friends came to the rescue and assisted the Academy in the purchase and remodelling of the first of its own buildings at 12 West 31 Street. Here, the library was housed properly along the walls of the new meeting hall, and its dominant position is indicated by the fact that the new auditorium was named Library Hall.

At first, the work of the Academy, even scientific work, was done through reference to special committees. During the first year, the Academy's concern was largely devoted to the protection of human life and welfare. A review of the activities of the year 1847 is most impressive. Quite appropriately, the very first committee was appointed to procure books for the library, another to investigate and report upon the use of sulfuric ether to mitigate pain in surgical operations and to make experiments on animals; still other committees were appointed in this year to investigate and report upon the subject of sewerage, to carry out investigation on an epidemic of typhus fever, to investigate the importation of adulterated and impure drugs, and (sic!) to study and report upon "the effects upon the human economy of milk from kine tuberculously or otherwise diseased from improper food or confined situations in (these) milk establishments." Although the cause of bovine tuberculosis was still a mystery to the good Founders of the Academy, they were already keenly aware of the hazard to human life involved in the consumption of milk from tuberculous and otherwise diseased cows and intended to do something about it. From these activities of the first year, it is clearly evident that the Founders were among the enlightened medical men of their time. That they were also men of courage and vision is indicated by their very first public actions, a memorial sent to the State Legislature urging the passage of a law for registration of births, deaths and marriages, another to the Congress urging legislation to control the importation of impure drugs, a third to

the State Legislature demanding State responsibility for the care of the feeble-minded.

In January 1848, a Committee on Public Health was appointed to study cholera and other epidemic diseases and to supervise the sanitary condition of the City. In subsequent years came action urging the State to separate medical teaching from medical licensure (1849) and another advocating the passage of a State law which would require that all medical schools be connected with hospitals (1850). There were annual memorials to the Congress which stressed the importance of vital statistics and urged that they be incorporated in the forthcoming Census. This was ultimately accomplished and, although the gathering of the information was imperfect, it represented the first attempt by the federal government to compile any vital statistics. The Academy was also instrumental in collaboration with the medical colleges in eliminating the practice of "body snatching" by aiding passage by the State Legislature in 1851 of the so-called Anatomical Bill which authorized human dissection.

During these early years, scientific papers were read at some of the monthly Stated Meetings, on such subjects as the treatment of ununited fractures, on "Revelations of the Microscope," and upon such extremely controversial matters of the day as the causes of inflammation and the relation of cleanliness of the physician to puerperal fever. On some of these subjects, long, heated discussions were sometimes continued through several successive monthly meetings. In 1850, the work of the Academy was officially subdivided among seven scientific committees but five years later, upon the recommendation of Dr. James Anderson, the By-Laws were again amended and the scientific work of the Academy was divided for the first time into Sections. The present sectional organization of the Academy is therefore 92 years old.

Ten years after it was founded (1857), the Academy made its first major contribution to the reduction of the enormous infant mortality of the time by studying the methods of production and the lasting qualities of concentrated milk. It found them satisfactory and endorsed concentrated milk as a safe and a valuable substitute for the extremely hazardous loose milk of that day and age. In 1861, the Academy called together the first sanitary convention to obtain reform of the laws pertaining to public health in this City and of their administration. This was only the beginning of a long series of annual efforts by the Academy, which

culminated in 1866 in the establishment of a Metropolitan Board of Health, the precursor of our modern Department of Health. Two of the Fellows of the Academy, Willard Parker and John O. Stone, served as the first Commissioners. In later years, when the City Department of Health was established, Commissioners of Health were repeatedly drawn from the Fellowship of the Academy, especially in times of crisis, the most distinguished being Griscom, Bryant, Goldwater, Emerson, and Biggs who served as General Medical Expert. In 1913, Biggs was largely responsible for rewriting the Public Health Laws of the State, which have since been copied by many other States. When the modern State Health Department was established in 1913, he became its first Commissioner, with Dr. Linsly R. Williams, later to be the first Director of the Academy, as his able Deputy.

It can be said with complete justice that Fellows of the Academy played leading roles in the creation in New York State of modern health services which became models for the country, and that the Academy as an institution has been a consistently powerful force in the organization and work of many governmental and voluntary health agencies, local and national, and in their early utilization of new discoveries in the medical sciences for the control of disease and the reduction of mortality. This has been increasingly true since the reestablishment of the Academy's Committee on Public Health Relations 36 years ago, under the Chairmanship of the late Dr. Charles A. Dana. Dr. James Alexander Miller was a charter member of that Committee and has been its Chairman for twelve years. Dr. E. H. L. Corwin has served continuously as its efficient Executive Secretary from the day it started 36 years ago. Under Dr. Miller and Dr. Corwin, the Committee has exercised a great creative influence in the Public Health history of this country. Its recent volume on Preventive Medicine in Modern Medical Practice is used by students in schools of medicine and of public health throughout the land. Its services are recorded in more than 900 reports and publications included in the current centennial exhibit on the History of the Academy in Room 21.

In 1876, the library was opened to the general public and from that time on, by agreement with the City, it has served as the medical part of the New York Public Library system. Later investigations by Academy committees led to improvements in the Croton water supply, in better methods of refuse disposal, in better State care of the insane,

and to at least some improvement of medico-legal testimony. In 1893, impelled by a serious cholera epidemic in the previous year, the Academy took the lead in initiating a successful nationwide movement to eliminate the ineffective quarantine responsibilities of commercially competing seaports and to establish for the first time a national quarantine service. It took years of effort before the Congress was persuaded to enact this obviously necessary legislation. Thirty-three years ago the Academy secured the passage of legislation which abolished the ancient but corrupt and inefficient system of coroners in the City of New York and on its recommendation, an Office of the Chief Medical Examiner consisting of qualified experts was established.

In 1930, in consequence of the inexcusably high maternal death rate, a three year study was begun by a subcommittee of the Committee on Public Health Relations with a paid field staff led by Dr. Ransom Hooker. The Department of Health promptly dispatched to the Academy a photostatic copy of the death certificate of every woman dying in childbirth, and an investigation was immediately instituted at the scene of the labor. The investigation included the family, the environmental conditions and the services of the attending physician, midwife, nurse, relatives and other persons who might have contributed to the result. After three years of patient work, it was found that two-thirds of all deaths in childbirth were preventable and that unnecessary interference or other medical errors by the attending physician was the most important factor in 45 per cent. The publication of these findings aroused a storm of violent criticism; medical societies and physicians in many parts of the country accused the Academy of injuring the reputation of the profession. Today, our county medical societies carefully review and censor the performance of the medical profession in this field. It is no mere coincidence that the maternal death rate dropped more than 66 per cent in the ten years immediately following the publication of the Academy's report. We in New York City can boast that today, about one-fifth as many mothers are lost in childbirth as 15 years ago. Under the influence of the new antibiotics, the decline in very recent years, is, of course, being accelerated. During the year 1946, there was a total of 152,736 live births in the City of New York, yet only 177 women died in childbirth from all causes. If this trend continues, childbirth may ultimately become safer than riding in an automobile or taking a bath!

In 1928, all national societies representing the various branches of medicine and all national governmental agencies concerned with the care of the sick were invited to assemble at the Academy for the purpose of establishing a National Conference on Nomenclature of Disease and preparing a Standard Nomenclature for use in hospitals and medical schools throughout the country. The work, which took 7 years to complete, was carried on within the Academy under its sponsorship, with funds made available to it by the Commonwealth Fund, the major life insurance companies and other philanthropic foundations. Since its publication the Standard Nomenclature of Disease has been adopted by medical schools and hospitals throughout the country and has had a profound influence upon the accuracy of medical terminology and of medical thinking. After the third edition had been issued, the American Medical Association graciously agreed to assume the responsibility for its continuing publication and revision.

In addition to these accomplishments, the medical provisions of the Workmen's Compensation Act of the State were rewritten at the request of the Governor by a Committee under the chairmanship of Dr. Eugene Pool. Through the Academy's Committee on Medical Education, wider educational opportunities have been provided for the continuing education of practicing physicians of the City by weekly practical lectures and demonstrations, by the meetings of the eleven Sections of the Academy, and above all, by the Graduate Fortnight which each year has attracted several thousand physicians. The Academy also serves as the educational information center for visiting physicians from other parts of the country, from Latin America and from overseas. In these postwar years, a special placement center has been conducted for the thousands of medical veterans returning from the Armed Forces who seek fresh educational opportunities in the large voluntary and Municipal hospitals of this metropolis before resuming medical practice.

The Academy's Committee on Medical Information has served for years as the information center for the public on medical matters. During the last two decades it has had a significant influence upon the accuracy of medical reporting by the press and the radio. Its public information bureau and its informative Lectures to the Laity reach many thousands. They are conducted in the tradition of the first anniversary discourse of the Academy delivered by Dr. John W. Francis in the Broadway Tabernacle on November 10, 1847, which attracted an

audience of more than 2500 persons and can be regarded as the Academy's first Lecture to the Laity.

I cannot close without reference to the monumental labors during the past four years of the Committee on Medicine and the Changing Order under the indefatigable leadership of Dr. Malcolm Goodridge and of the Committee's versatile secretary, Dr. Iago Galdston. Within the last two years, the Committee has published a preliminary series of 10 monographs which cover almost all aspects of contemporary problems of medical care. The work of this Committee, which included eminent non-medical and medical leaders, has culminated this month in the publication of a volume embodying its Report and Recommendations on the changes in medical practice and medical education and in the methods of paying for medical care which will be required to make the benefits of modern preventive and curative medicine available to all families of low income. This volume, published by the Commonwealth Fund, is a timely document, for it points the way to far reaching changes which can be made without jeopardizing the high level of performance achieved by American medicine during the last three decades. In my opinion, the work of the Committee on Medicine and the Changing Order represents the pinnacle of the Academy's achievements. Its publication in this Centennial year is a happy and appropriate coincidence.

It should also be a source of pride to the Fellowship that the Secretariat of the World Health Organization of United Nations accepted the hospitality of the Academy last summer immediately following its establishment by a conference of delegates from seventy nations of the world. During the summer and fall of 1946 we were privileged to provide space for the staff of the Interim Commission until permanent headquarters became available. The Academy has therefore had the honor of being the first home of the World Health Organization of United Nations.

It is now important that the Fellowship arrive at an understanding concerning the main lines of activity along which the work of the Academy is hereafter to advance. The Library must maintain its present position as the most useful and influential depository of medical and related scientific literature in the world. This will require the immediate erection of a new building for additional book stacks and reference files, for the Library is now bursting its seams. The overworked library staff must also be materially expanded if the efficiency of their services

to the Fellows and to the public is ever again to equal that of the prewar period. These two objectives will require additions to our present building fund and a substantial increase in endowment. I would remind you that the income from annual dues of the Fellowship at present provides only one-fifth of the operating budget of the Academy and that recent increases in salaries, chiefly of the lowest paid workers, will in 1947, unbalance the rigidly restricted budget by \$90,000. To meet these needs, we are entirely dependent upon the generosity of an informed public as well as of the Fellowship.

The second most important future activity of the Academy is in the field of medical education. The continuing education of physicians is a major concern of the Academy, not of the medical schools which are already heavily burdened with undergraduate medical education and with graduate training in the specialties. The great system of voluntary and municipal hospitals of New York at present provides almost one-fifth of all the grade A internships and residencies of the country. In collaboration with the five medical schools of the City, the Academy will serve as the centralizing agency and will, I hope, assume an even more important role than heretofore in improving the educational curricula of interne and residency training. The internship and residency period should provide the young physician with an educational and scientific environment in which he can attain his maximum professional and scientific growth. Through its influence upon the hospitals, almost all of whose senior staff members are Fellows, the Academy can in this manner materially influence the future level of medical practice.

The Academy with its exceptional physical and intellectual resources is strategically located in this metropolis to assume, also, an even greater measure of responsibility in the future than in the past for elevating the general level of medical practice through a comprehensive program of continuing education which must follow the internship and residency training of all physicians until the end of their lives. During the next years, the Academy proposes to weld together the resources of the 65 major hospitals of this great City so as to make it the center of medical education for the physicians of this Nation and of the world. Under the plan we have in mind, New York will become the medical capital as it is already the political capital of the world.

In these educational activities, the eleven clinical and scientific Sections of the Academy must play a more important part than in the past,

each for its own specialty of medicine and surgery. In addition, it will probably be necessary to organize several new Sections devoted to the related basic sciences or to accomplish a closer working relationship with some of the affiliated scientific societies, many of which now meet in the Academy building. At the request of a score of eminent scientists, the Council of the Academy is at present considering the establishment of a new Section on Microbiology which will encompass bacteriology, immunology, parasitology, virology and chemotherapy.

In extending its teaching activities in this manner, the Academy will be required to expand its physical facilities by constructing an addition to the east. This building is to replace the three adjacent tenements on 103rd Street, which we now own. The plans for this extension have been drawn by Mr. Edwin A. Salmon, Chairman of the City Planning Commission. The architectural rendering will be exhibited during March and April in the Academy's Centennial Exhibit on Hospitals in Room A. The proposed exhibit halls will be devoted to visual education through the medium of medical exhibits on matters of vital current importance. These exhibits will be frequently replaced with new material illustrating the most recent advances in medicine and medical technology, and will supplement the didactic and bedside teaching throughout the city. The upper floors of this building are designed to house the staff of the Committee on Medical Education of the Academy through which a city-wide educational program can be administered. In addition to exhibits for the instruction of physicians, the building will also be used from time to time throughout the year for exhibits designed for the education of the general public. The execution of these plans and the erection of the proposed addition will be undertaken as soon as the necessary funds become available for construction of the new addition and for its maintenance. It will require \$500,000 for the building and the addition of \$1,000,000 to the Academy's endowment.

A third new activity of the Academy has also been approved by the Council. It involves a continuing study of social and environmental factors responsible for illness and mortality, and of the changes in methods of medical practice and medical education which may be necessary before the full benefits of modern curative and preventive medicine can be made available to all the people. With the authorization of the Council, I shall shortly appoint a new Committee on Medicine and the Changing Order for this purpose. This Committee will also concern

itself with preventive psychiatry, social pathology and social medicine, a field which promises to reveal new and ever broader opportunities for public service. Because the terms social pathology and social medicine are still generally misunderstood in this country, we have persuaded Professor John A. Ryle to visit us from across the seas to give us a definition of their meaning and a better understanding of their scope.

A recital of the names of former officers and Fellows who have served the Academy would read like a succession of pages out of the medical history of the country. Following John Stearns, the early presidents included John W. Francis, Valentine Mott, Isaac Wood, Alexander H. Stevens, Thomas Cock, Joseph M. Smith, Willard Parker, John Batchelder, John Watson and James Anderson. After the Civil War came Austin Flint, Samuel S. Purple, B. Fordyce Barker and Abraham Jacobi; then Loomis, Roosa, Bryant and Janeway.

I shall not mention all the distinguished presidents of our own generation except to state that among others, it was Jacobi who saved the Academy during a crucial period 60 years ago when its continued existence was in jeopardy and it was Jacobi and Loomis who later were largely responsible for the erection of our third home on West 43 Street. In addition to Walter B. James, George David Stewart, Samuel A. Brown, it was Bryson Delavan, Arthur B. Duel and our first executive director, Linsly A. Williams who built the beautiful structure which we now occupy, and laid the paths to public service which we now follow. I grieve that Linsly is not with us tonight to share our joy in his accomplishments. Our building is his monument; our deeds will be the measure of our appreciation of his noble character and his life of service to human welfare. I must confess that his great spirit has long been my guide and inspiration.

To these men and to our own beloved Samuel Lambert, John Hartwell and Bernard Sachs, we stand forever indebted. It is with mingled emotions of affection and deep gratitude that, through my inadequate voice, the Fellowship here assembled acknowledges its debt to the past presidents of the Academy who are with us tonight, or are listening to this broadcast, Samuel A. Brown, Eugene Pool, James Alexander Miller, Malcolm Goodridge, Arthur Chace, and to our recent Director, the amiable and efficient Herbert Wilcox. I know that I echo your own feeling of profound admiration when in your name and as an expression of your appreciation, I pledge them our devotion to the aims and ideals of the Academy.

RECENT STUDIES ON THE FUNCTION
OF THE ADRENAL CORTEX*

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THE science of endocrinology is developing in a manner paralleling that of its sister sciences. That is to say from its beginning as merely a description of the phenomena attending the loss or excess of an internal secretion, it is passing by slow degrees to a study of the manner in which these secretions regulate the metabolic processes of the cells upon which they act. For it cannot be too strongly emphasized that the hormones do not initiate new patterns of cellular function, these are an inherent birthright of the cells themselves. All that any hormone does is either to facilitate or inhibit certain types of chemical transformations within the cells. The manner in which this is accomplished remains one of the most fertile fields for further study. Speculation as to the role of hormones in biological processes ranges all the way from the view that they are direct participants in enzyme actions to the more obscure hypothesis that they act as organizers of cellular activity. It is evident, however, that the future development of endocrinology will be inextricably combined with that of our knowledge of the chemical transformations or intermediary metabolism of cells. Indeed it is fair to suggest that "biochemical endocrinology" offers at the present time the most promising field for the elucidation of hormonal activity.

This evening, I have elected to speak on various studies carried out in the last few years to illustrate the value of the biochemical approach to the study of the function of one endocrine gland—the adrenal cortex.

There are three basic questions that require to be answered before we can be said to possess a full understanding of the function of any endocrine organ. These are:

1. What is the chemical nature of the hormones secreted by the gland? To answer this we must proceed from the isolation of the hor-

* Presented at a meeting held under the auspices of the New York Diabetes Association, Inc., on Saturday, January 11, 1947, at Blumenthal Auditorium, Mount Sinai Hospital, New York City.

mone from the gland in pure form, to the determination of its structure. In some instances, this has been followed by the complete or partial synthesis of the active principle. In the case of the protein hormones this last step is still only a future possibility.

2. What are the conditions under which the gland in particular is called upon to secrete increased quantities of its hormone? That is to say what particular circumstances arising within or without the organism require an increased usage of the hormone by the tissues upon which it acts. This question resolves itself into two parts: (a) what is the mechanism, humoral or nervous that activates the secretory processes of the gland, and (b) what are the chemical transformations within the gland that accompany the release or formation of the hormone.

3. In what way does the hormone affect the metabolic activities of the cells upon which it acts? I again repeat that we only recognize the effects of hormones through the alterations they produce in the rate of certain cellular processes. Even such obvious effects as increase in body size, abnormal hirsutism, etc. are of necessity accompanied by metabolic changes. Some of these associated metabolic changes are the most easily recognized evidences of hormonal activity, others are still unknown but we may with some assurance assert that they exist.

In all three of the above categories, chemical nature of the hormone, conditions of secretion and mechanism of action, substantial progress has been made in recent years in our knowledge of the function of the adrenal cortex. Let us now consider these in the above order.

CHEMISTRY OF ADRENAL CORTICAL HORMONES

The pioneer studies of Stewart and Rogoff, and of Hartman had indicated that various types of adrenal cortical extracts could effect a moderate prolongation of the life of adrenalectomized animals. The recognition that the activity resides primarily in lipid extracts of the gland and that such extracts could indefinitely prolong the life of adrenalectomized animals is to the credit of Swingle and Pfiffner. Their methods of extraction furnished the starting material for all subsequent isolations of the active principles.

These active principles were soon recognized to belong to the great class of chemical substances known as steroids. The isolation of these and some twenty others, not possessing biological activity is due to the

work of Pfiffner, Wintersteiner and Kendall in this country and to that of Reichstein in Switzerland. The wealth of steroid material present in these glands, both in number of compounds and the diversity of their action, exceeds that found in any other organ of the body, not excluding the gonads, which in their capacity as endocrine glands also secrete steroid hormones. Why the adrenal cortex should contain and presumably manufacture not only the steroids with the characteristic activity of this organ, but also those with gonadal activity, as well as a large number with no known biological activity, is but one of the unsolved problems of its function.

The minute concentrations in which the active steroids of the adrenal—the corticosterones—are present in the gland has made it difficult for investigators to carry out the number of experiments with the pure hormones that they have desired. The generosity of those who have laboriously isolated, and then donated these valuable compounds to their colleagues for their work is beyond praise, and as one of the recipients of their kindness I am happy to acknowledge how much it has meant to our work.

It is also a matter of gratification to know that the partial synthesis both of dehydro corticosterone and 11-dehydro-17-hydroxy corticosterone from desoxy cholic acid has now been accomplished. This important work is the result of the collaboration of a number of organic chemists in different parts of the country. The combined efforts of Wallis of Princeton, Kendall of the Mayo Clinic, Gallagher at Chicago, Riegel at Northwestern, Wintersteiner at the Squibb Research Institute and Sarett of the Research Laboratories of the Merck Company have resulted in the preparation of quantities of the synthetic hormones far exceeding those ever available from natural sources. The importance of this to the further conduct of research in the field of adrenal physiology is obvious while the potential value of these new synthetic hormones in the treatment of human disease can now, for the first time, really be explored.

CONDITIONS ASSOCIATED WITH INCREASED ADRENAL CORTICAL SECRETION

The manner in which the activity of the adrenal cortex is adjusted to the needs of the organism and the circumstances which call forth an increased secretion of its hormones is a problem engaging many investi-

gators at the present time. As I mentioned above, one of the tenets of present day endocrinology is that the endocrine glands do not act in an independent and haphazard manner but adjust their secretory rate very closely to the actual needs of the moment.

The second question to be answered is: "What are the factors that regulate the secretory activity of this gland?" This requires for its solution the development of methods that will tell us when the gland is actually producing its hormone at an accelerated rate.

As regards this question a good deal of information is now available. In 1930, P. E. Smith showed that removal of the hypophysis in the rat was followed by atrophy of the adrenal cortex and that this could be prevented by the injection of crude pituitary extracts or by implants of the anterior pituitary itself. A large amount of work has since shown that all conditions that cause adrenal cortical enlargement, and these are too numerous to mention, fail to do so in the absence of a factor from the anterior lobe of the pituitary. This factor is a protein hormone now known as the adrenotrophic or corticotrophic hormone. It has recently been isolated from the anterior lobe in a highly purified, if not completely pure form by workers in two laboratories. Such a preparation has been obtained from sheep glands by Li, Simpson and Evans and from hog glands by Sayers, White, and myself.

It is interesting to report that these two groups, working independently and with the pituitaries of different species isolated a substance whose biological, chemical and physical properties agreed in a remarkable manner.

When injected into animals this trophic hormone produces all the effects given by the cortical hormones themselves. Thus it has been found that it brings about an increased level of liver glycogen and of urinary nitrogen excretion. It causes glycosuria, sodium retention, and increased potassium excretion in rats, and has an effect identical with that of the corticosterones in reducing the number of circulating lymphocytes. All these effects can be evoked in the hypophysectomized animal in which no other known agent will cause an increased adrenal cortical secretion. So far as is known at the present time the only effect of this hormone is the stimulation of the secretory function of the adrenal cortex.

However, while the identification and isolation of this trophic hormone answers the question as to the agent responsible for an increased

adrenal cortical secretion it merely transfers to the anterior lobe of the pituitary the question as to the mechanisms that cause this gland to secrete the agent that is essential for an increased hormone production by the adrenal cortex. Are these mechanisms of nervous or humoral origin?

Before such a question can be experimentally tested it is necessary to have available some method of determining the rate of secretion of the adrenal cortical hormones. When we began our studies the available methods for following adrenal cortical secretion were not very suitable for studies in which small animals were to be exposed to a variety of conditions. Those that had been used included (a) the determination of "cortin" excretion in the urine by chemical or biological methods. This is obviously impracticable in small animals although in man it has been successfully used by Browne and Venning and others to show that trauma or infections increase the secretory rate. (b) Direct determinations of cortical hormone by biological methods in the blood of the adrenal vein. This method, applicable only to dogs under anesthesia, had been used by Vogt in England. It has yielded important information including the demonstration that epinephrine injection or the administration of glucose forming but not non-glucose forming amino acids is followed by an enhanced output of the hormone. (c) Methods based on the actual content of hormone in the gland. These are not practical at the present time.

Consideration of the question led to the suggestion that some lipid constituent of the gland might vary with different degrees of its activity. It was known that the stainable lipid of the gland decreased under conditions associated with increased secretion, also there was some evidence that the cholesterol content of the gland underwent similar changes. Indeed, there was a voluminous literature on this last subject, containing many contradictions and expressions of opinion as to the relation of adrenal cholesterol to the intermediary metabolism of this substance in the rest of the organism. The general idea that cholesterol might be the precursor of the steroid hormones has also been put forth by various investigators but curiously enough no experiments to demonstrate that it varied under conditions of increased secretion of the adrenal cortex or gonads had been done.

We, therefore, injected the highly purified preparations of adrenotropic hormone into rats and determined the cholesterol content of

the glands after various intervals of time. It was found that single injections of this trophic hormone decreased the cholesterol content of the adrenal by some 50 per cent in three to six hours, while its return to normal levels required many hours. Similar results were observed in hypophysectomized rats, provided too long a time had not elapsed since the operation. The cholesterol content of a variety of other tissues was not affected by such injections. As will be seen later, exposure of animals to such stresses as cold, burns, trauma or hemorrhage brought about similar alterations in the adrenal cholesterol of normal rats but did not alter the level in hypophysectomized animals. Evidently the natural secretion of adrenotrophic hormone following such procedures can also be detected by the changes in the cholesterol content of the adrenal.

In reviewing these results it appeared entirely possible that the rather long period, an hour or more before the adrenal cholesterol fell significantly, might be due to the fact that this substance acted as a reservoir for the continual replenishment of the hormone itself and that other substances in the gland might be more closely related to the actual secretion.

The adrenal cortex is also unique in its high content of ascorbic acid (Vitamin C). Furthermore, this gland and the corpus luteum are the only tissues in which such a high concentration of the vitamin is found along with a very high concentration of cholesterol in the ester form. It is unnecessary to remind you that ascorbic acid was originally isolated from the adrenal although the reasons for its presence in such large amounts were not known. Further study of the literature indicated that as in the case of cholesterol the level of this vitamin in the adrenal was subject to wide variations, it being notable that under conditions of stress low values were found.

Consequently, similar experiments were carried out with adrenotrophic hormone and it was found that the ascorbic acid level of the adrenal fell very promptly after the injection, reaching values of less than 50 per cent of the original level within one hour. Indeed, a significant decline could be detected within 20 minutes after injection. Exposure of normal animals to the types of stress mentioned above was followed by marked reductions in adrenal ascorbic acid yet similar treatment of hypophysectomized animals failed to affect the level of the vitamin in the gland. The ascorbic acid content of other tissues

was not affected either by adrenotrophic hormone or by exposure of animals to conditions that were followed by a decline in its content in the adrenal.

While it might be argued that these changes in adrenal cholesterol and ascorbic acid are only indirect measure of adrenal cortical secretion, our experience has convinced us that they furnish a reliable and rapid indicator of this secretion. As I have pointed out above, it is apparently mediated by the preliminary passage into the blood stream of additional quantities of the pituitary adrenotrophic hormone. Even if these changes in adrenal cholesterol and ascorbic acid were not directly associated with the elaboration and secretion of the cortical hormones but were merely expressions of a general heightening of adrenal metabolism, they would still be of value for following the secretory activity of the gland. However, there is other evidence that more directly links these changes in adrenal chemistry with the actual formation and release of the cortical steroids. Bloch and Rittenberg have shown by the use of cholesterol tagged with deuterium that not only the bile acids but also progesterone are formed with this steroid. The structure of progesterone is sufficiently akin to that of the corticosterones to make it extremely probable that the latter also are formed from cholesterol.

At least one role of ascorbic acid in the adrenal would appear to have been clarified by the recent report of Lowenstein and Zwemer that it is possible to isolate from this gland a water soluble and biologically active steroid in which the steroid nucleus is apparently linked to ascorbic acid. If this is correct then ascorbic acid is actually a part of the hormone in the form in which it is secreted by the gland, cholesterol presumably furnishing the material from which further quantities of the steroid portion may be elaborated as it is required.

The association of a vitamin with a hormone in this manner is the first known example of a common point of activity of members of these two important groups of substances, although examples of vitamins forming portions of co-enzymes are now fairly numerous. The recent report of Price, Colowick, and Cori on the influence of insulin, anterior pituitary and cortical hormones on the activity of the enzyme hexokinase is an outstanding instance of such interplay, particularly since nicotinic acid amide is a component of the hexokinase system. In this system, a hormone, vitamin and protein enzyme are all part of a cellular mechanism for carbohydrate metabolism.

Finally, it may be pointed out that there is an excellent degree of correlation between the decline in adrenal cholesterol and ascorbic acid and such tangible and well authenticated manifestations of adrenal cortical activity as the increase in liver glycogen in fasting animals and the fall in the number of circulating lymphocytes.

It is, therefore, possible not only to use these changes in the chemical composition of the adrenal as indicators of increased secretory activity but also under the right conditions to employ them as a method for the assay of the adrenotrophic hormone itself. For this last purpose it is desirable to use hypophysectomized animals as the test objects since their adrenal cholesterol and ascorbic acid will only be affected by the trophic hormone and not by any non-specific agent in the material injected. By the use of such a method Dr. and Mrs. Sayers have found that a rat pituitary gland contains about 20 micrograms of the hormone. It should now be possible to apply this method to the determination of the level of adrenotrophic hormone in the body fluids, a procedure that should be of particular value in the diagnosis of certain endocrine disorders in man.

We have already made a considerable number of observations on the effect of various procedures on the secretory activity of the adrenal cortex. In most of these experiments we have been satisfied to determine only ascorbic acid since it reflects any change more rapidly than cholesterol. We have found that exposure to cold (4° C. for one hour) hemorrhage, trauma to muscles, and particularly to the long bones, painful stimuli, cutting or bruising the skin, burns, the intraperitoneal injection of cold isotonic saline or other fluids, and the inhalation of volatile anesthetics, all cause an immediate and prompt increased rate of secretion of the cortical hormones. As might be expected the degree of activation of the gland is determined by the intensity and duration of the stimulus applied.

We come now to an interesting and important point concerning the manner in which these diverse types of stimuli bring about an increased degree of cortical secretion. Three recent investigations bear on this point.

(a) We have found that epinephrine which is certainly released after the most varied types of stress, causes within an hour after subcutaneous or intravenous injection a decrease in adrenal ascorbic acid in normal rats but not in rats 3 days after hypophysectomy. The

amounts required are within the physiological range.

(b) Vogt also has found that epinephrine causes a marked increase in the quantity of cortical hormone in the adrenal vein blood of dogs. However, in one experiment on a decapitated dog she reports that epinephrine also caused an increase and in a private communication she informs me that it also augments the output of the isolated, perfused adrenal of the dog. Nevertheless, in chronic experiments, epinephrine produced adrenal hypertrophy only in normal but not in hypophysectomized rats.

She concludes that the effect of epinephrine is a direct one on the secretory cells, independent of the anterior lobe and that the absence of an effect of epinephrine in rats injected from the 3rd to the 12th day after hypophysectomy is due to the degeneration of the glands caused by lack of corticotrophic hormone.

In other words Vogt and ourselves are agreed that epinephrine is a potent stimulus to adrenal cortical secretion, although we differ as to its mode of action.

It is possible to devise more decisive experiments to settle this point but whatever may be the answer it is of importance that either directly, or indirectly through the adrenotrophic hormone, the stimulation of the sympathetic nervous system and consequent liberation of epinephrine is capable of increasing cortical hormone output. Such sympathetic activity is always a component of these varied circumstances that are known to call forth such secretion by the cortex. Heat, cold, hemorrhage, trauma, burns, toxic agents, and painful stimuli of all kinds are always associated with an increased degree of activity of the sympathetic nervous system. Consequently it may be assumed that this is at least a very important if not the only means by which an augmented supply of cortical hormone is released to meet these states of emergency.

I am also aware of the implications of the statement that epinephrine can cause stimulation of the adrenotrophic function of the anterior pituitary. For if it is an agent in this regard then it must act either by the stimulation of adrenergic cells in the anterior lobe, nerve cells whose existence is equivocal, or directly upon certain sensitive cells in the gland itself, after the manner in which it accelerates glycogenolysis in skeletal muscle.

(c) A third set of experiments expressing another point of view, or rather another mechanism by which adrenal cortical secretion is regu-

lated has recently been published by Dr. and Mrs. Sayers.

They have found that prior treatment of rats with cortical hormone prevents the usual fall in ascorbic acid when the animals are exposed to cold. We have confirmed this and shown that such treatment also prevents the fall in adrenal ascorbic acid not only after painful stimuli, trauma. etc., but also that usually produced by epinephrine. I have no doubt that the effect of other types of stress on this component of the adrenal can also be prevented by prior treatment with cortical hormone. Sayers and Sayers suggest that the blood level of cortical hormone determines the secretion of the adrenotrophic hormone. A decline in the former, presumably caused by the stress applied to the animal acts as a stimulus to the secretion of the latter. If the fall in the blood level of cortical hormone is prevented by injection of exogenous cortical hormone, then the pituitary does not respond. In other words, a differential and temporary hypophysectomy is achieved by this means.

These experiments imply that stress produces conditions that cause an increased rate of utilization of cortical hormone in the tissues. This in turn brings about a reduction of the blood level of this hormone which is the exciting factor to the anterior pituitary. Such a view is perhaps half way between that of Vogt and ourselves. It regards the adrenotrophic hormone as the essential factor for cortical secretion but relegates epinephrine to a place with other non-specific types of stress that reduce the blood level of cortical hormones. Although our experiments indicate that the stimulating effect of epinephrine on the pituitary (if this exists) is abolished by raising the blood level of cortical hormones, it must be remembered that epinephrine itself is a hormone with well defined points of action and is not in the usual sense "a non-specific agent." However, it is also possible that the well known metabolic effects of epinephrine may cause an increased utilization of cortical hormone by the tissues or change the composition of the blood passing through the anterior lobe. Only further experimentation can settle these controversial points but I again repeat that the fact that epinephrine, by whatever mechanism, increases the secretion of cortical hormone is in itself a point of some importance in our understanding of the means by which the organism adapts itself to stress. Indeed this observation furnishes an interesting corollary to the emergency theory of adrenal medullary function put forward by the late W. B. Cannon.

Even with these points unsettled the picture of the control of

adrenal cortical secretion appears at the present time to be as follows:

(a) The changes in adrenal ascorbic acid and cholesterol may be used as indicators of cortical activity. The former is probably directly related to the secretion of the hormone, the latter acting as a reservoir of the precursor of the hormone.

(b) The various circumstances that increase the cortical secretion do so in all probability by first activating the adrenotrophic secretion of the anterior pituitary.

(c) The manner in which anterior lobe activation is affected is either by a decrease in the blood level of cortical hormone or some other unknown changes in the composition of the blood traversing the gland.

(d) The release of epinephrine, which occurs in so many circumstances, increases adrenal cortical secretion. It may do so (1) either by a direct effect on the gland (which is Vogt's view), (2) by stimulation of the anterior pituitary, (3) as a result of its own effects on the composition of the blood passing through the pituitary.

The series of events just outlined is a good example of the correlation and interplay of three components of the endocrine system, anterior pituitary, adrenal cortex and medulla. Their combined operation facilitates the adaptation of the organism to external and internal stresses, stresses which if unchecked would threaten its continued existence. Their operation not only corrects changes in the fluid environment that are detrimental to cellular function but also creates conditions within the environment and the cells that are best adapted to meet the emergency.

MECHANISM OF ACTION OF ADRENAL CORTICAL HORMONES

I would now like to turn from a consideration of the regulation of adrenal cortical activity to the equally complicated question as to the manner in which the hormones of this gland produce the observed metabolic changes in the cells and body fluids. For it must be in their capacity to facilitate certain types of cellular activity that the protective properties of these hormones reside.

This evening, I have not time, nor do you have the physical endurance, to listen while I review the large amount of work that has been done on the function of the cortical hormones. I can but remind you that these hormones are particularly active in the regulation of many

phases of metabolism. Thus, they regulate the sodium, potassium and water balance by their influence on the rate of kidney tubular excretion and reabsorption of these ions and in this way control the shift of fluid and electrolytes between the various compartments of the body. As is now well known these hormones also have a marked effect on several phases of the organic metabolism. It was recognized many years ago that a subnormal blood glucose level is a frequent finding in adrenal insufficiency in animals and man. Britton has shown that the other carbohydrate constituents of the body, notably the liver and muscle glycogen are depleted and that the injections of the cortical hormone, even without food rapidly restores these levels.

In spite of this, it was soon surmised that neither the control of the electrolyte or carbohydrate levels fully explained the action of the hormone. For while it is true that adrenalectomized animals or humans with adrenal insufficiency might die from electrolyte loss or carbohydrate depletion, the mere administration of sodium salts or carbohydrate was not sufficient to return them to a normal state, even though life might be extended by their use.

In 1934 Lukens and I found that adrenalectomy alleviated many of the consequences of total pancreatectomy in the cat and dog. The most notable effect, apart from a prolongation of life was the reduction in urinary glucose and nitrogen excretion, a fall from the characteristically high to more normal blood glucose levels and a striking abatement of ketosis.

The general conclusion concerning these metabolic changes was that adrenalectomy reduced the high rate of conversion of tissue proteins to glucose (gluconeogenesis) while at the same time it allowed a higher rate of carbohydrate utilization. The converse conclusion would be that the adrenal cortical hormones accelerated the conversion of tissue proteins to glucose and/or inhibits carbohydrate utilization by the tissues. Indeed, Vogt has recently shown that infusion of amino acids forming glucose in the body increased the requirement for cortical hormone but the non-glucose forming amino acids do not.

Later experiments demonstrated that in other conditions accompanied by a high rate of gluconeogenesis from protein, adrenalectomy was followed by a comparable reduction in the quantity of protein undergoing catabolism. It has since been shown in several laboratories besides our own, that the injection of either the cortical steroids or adreno-

trophic hormone into normal fasting animals increases the rate of protein breakdown to a marked degree, while at the same time, large quantities of glycogen are deposited in the liver. In fed animals, as Ingle has shown, actual glycosuria follows prolonged injection of either of these hormones, indicating that carbohydrate utilization was also suppressed.

The adrenal cortical hormones by their capacity to accelerate the catabolic phases of protein metabolism retard the growth of growing animals. They, therefore, stand in opposition to the growth promoting factor of the pituitary, which promotes the retention of protein in the body. Since the activities of the adrenal cortex is also regulated by the anterior pituitary, this gland exercises control over the rate of both the catabolism and anabolism of protein.

However, it will be appreciated that though we use such terms as "promotion of gluconeogenesis," "stimulation of protein catabolism," "inhibition of carbohydrate utilization" to describe the function of the adrenal cortex, we have not yet succeeded in completely defining the action of these hormones. It is true that a stimulation of glucose formation along with a suppression of tissue utilization of carbohydrate is an important factor during periods of fasting. Furthermore the present concept of a dynamic state of protein metabolism indicates the necessity for the regulation of catabolism as well as anabolism. In spite of all these examples of the teleological significance of the hormone there is still one feature of adrenalectomized animals that requires consideration before we can accept any present hypothesis as a complete explanation of the function of this gland. This is the remarkable inability of adrenalectomized animals to withstand alterations in the external or internal environment that are easily tolerated by intact animals. This intolerance is too well known to need further description but it should be remembered that merely correcting the disturbances in the sodium or carbohydrate metabolism by administration of these substances is not sufficient in itself to insure survival.

These measures while they may bring about the extended survival of adrenalectomized animals living under quiet undisturbed conditions of existence, fail conspicuously to protect such animals under conditions which are easily tolerated by normal animals. Only the cortical hormones can confer a normal resistance to stress to either adrenalectomized or hypophysectomized animals.

This fact and many more that might be enumerated, for example

the effect of the hormones on the early fatigue of the skeletal muscles, so well described by Ingle, indicate that there still remains to be found some other basic mechanism of their action. The effects of adrenal cortical insufficiency are extended to many organs, each of which expresses this insufficiency in terms of its inherent function. Thus we observe the rapid fatigue of working muscles, inadequate intestinal absorption, reduced ability of the kidney to separate sodium and potassium, and such defects in liver function as a decreased rate of gluconeogenesis. Yet even with such evidence of the necessity of cortical hormones for the proper function of so many different organs we must assume, until it is proved otherwise, that in each organ the point of action of the hormones is the same. At the moment we do not know, except in general terms, what this effect is. All we can say is that without these hormones the capacity of many types of cells to perform their particular function is impaired, and that this becomes particularly evident in times of stress.

Recently some new observations on a well known effect of cortical hormones have been reported which indicate, if further proof were needed, that we have still much to learn about their action in the body.

Those of you who are familiar with the beautifully illustrated monograph by Thomas Addison in which was first clearly defined the relationship of the adrenals to the disease in man which now bears his name, will remember that one plate shows the remarkable enlargement of the abdominal lymph nodes in the cases he described.

Since that time, numerous observations both in man and animals have made us aware of the reciprocal relationship between the adrenal cortex and the lymphoid elements of the body. Withdrawal of the hormone is associated with lymphoid enlargement; an excess of hormone causes rapid involution of these elements. This relationship has been particularly emphasized by Selye in his many papers describing the phenomena associated with the "alarm reaction." This investigator has shown that a variety of insults to the organism cause, along with adrenal cortical hypertrophy, a rapid involution of the thymus and lymph nodes.

Dr. White in my laboratory* in association with Dr. Dougherty of the Department of Anatomy at Yale have recently made a more detailed analysis of this relationship. Their results may be summed up as follows:

* The investigations reported in this paper from the Yale Laboratories were supported by a grant from the Field Research Fund of the Yale University School of Medicine.

(a) The number of circulating lymphocytes is under pituitary-adrenal control. That is to say that when the cortical hormones or the adrenotrophic hormone is injected into normal animals they cause a rapid decrease in the blood lymphocytes reaching a maximum a few hours after injection.

(b) The reduction in the blood lymphocytes is not due to an increased rate of withdrawal by the tissues but is brought about by a rapid lympholysis in the lymphoid tissues themselves. This is further emphasized by the experiments of Reinhart who found a 50 per cent reduction of lymphocytes in the thoracic duct lymph within twenty minutes after the injection of adrenotrophic hormone.

(c) This lympholysis liberates into the lymph and ultimately into the blood serum the contents of the lymph cells. One of these constituents has been identified as normal serum gamma globulin, a second is probably serum beta globulin. The rise in total serum globulin, due almost entirely to these two globulins has been shown by electrophoresis of the serum of treated animals.

These experiments indicate an entirely new effect of cortical hormones on protein metabolism. For by this action, intact cellular protein molecules are translocated through the body fluids to all parts of the organism. As in all instances of hormone action this process is not initiated by the hormone but merely altered in the rate at which it proceeds. Once dispersed in this manner this protein may be metabolized by the different tissues in a manner best suited to their requirements; these presumably vary according to their function.

(d) Since it is well known that the gamma globulins are the fraction of the serum proteins that carry the specific immune bodies, White and Dougherty immunized animals to various antigens both with and without the injection of cortical hormones. In all cases the titre of the specific antibodies in the serum rose faster and to higher levels in the group receiving the hormone. But this was not all. For if the injection of both hormone and antigen was stopped and sufficient time allowed for the serum titre of antibody to largely disappear, the injection of a single dose of cortical hormone caused in a few hours, antibodies to reappear in the serum to levels reached during the height of immunization. Exposure of immunized animals to any stimulus that causes adrenal cortical secretion was followed by similar rapid increases in serum antibodies. In other words this "anamnestic reaction" is a mani-

festation of the control of lympholysis and serum globulin release by the cortical hormones.

It is apparent that the release of immune globulins in immunized animals is merely a special case of a general phenomenon, for similar quantities of non-immune globulins are released along with other cellular materials from the lymphocytes of non-immunized animals. Yet in the immunized animals, the actual release of cortical hormones confers a specific resistance to a particular infecting agent. Is there then a relationship between the lympholysis occurring in non-immunized animals and their resistance to such non-specific stimuli as heat, cold, trauma, etc.? Is such non-specific resistance determined, at least in part by the capacity of the cortical hormones to liberate from the lymphoid elements into the circulating fluids substances that are vital to the cells for a successful defence against the distortion of their internal environment? This is an unanswered but important question but these experiments have opened an entirely new line of thought not only concerning the inability of adrenalectomized or hypophysectomized animals to contend with the factors that distort their internal environment, but also as to the mechanism of action of the cortical hormones. If nothing else they lend emphasis to the point that there are still unexplored fields in our knowledge of the function of the adrenal cortex.

DISCUSSION

DR. ROBERT F. LOEB: I think we are all very priveleged to have heard a most stimulating and provocative talk by Dr. Long. I think the most important thing is that we congratulate him and his coworkers on the contributions which they made to our understanding of the functions of the adrenal cortex. Anything which I might say after this is pretty much of an anticlimax. but I will make my climax very brief.

There is one point which Dr. Long introduced early in his talk which I should like to emphasize very strongly and that is the question of just what the role of the endocrine glands may be. We are all pretty much interested in them these days, and I think he put his finger on a very important point when he emphasized that they function primarily to facilitate or inhibit certain cell activity and probably not to be primary regulators.

I believe it is terribly important for us to remember that even the

lowly malarial parasite has a perfectly good anaerobic and aerobic glycolytic cycle which my friends tell me they cannot distinguish from that of man, and yet to the best of my knowledge, the malariologists do not associate a pancreas, a pituitary and a duodenum with the malarial parasite. Still it carries on. It grows, oxidizes and divides without an endocrine system, and perhaps it is well to look on the endocrine system as a very important superstructure which is introduced as an expediting system, as Dr. Long has said, to facilitate or inhibit certain fundamental activities in a very complicated organization of society of cells such as exists in higher animals.

One of the other very important, very exciting parts of this work, to say nothing of the work concerning the potentialities for measuring concentrations of hormone in blood, at the present time is what Dr. Long emphasized, namely, the opening up of a vista concerning the interrelationship of the hormones and vitamins, the central nervous system for instance and the enzyme systems themselves. It seems to me that if one is going to strike at the heart of the problem of the hormones that more work must be directed towards this end.

The clinician has one point, which I should like to emphasize too, and that is, I think in certain ways we have harder times than do the biochemists and physiologists. They work with small animals. We work with the large one. We all know the importance and easily demonstrated factors of protein-carbohydrate disturbances in animals and the response of small animals to the administration of the 11-oxy- or 17-hydroxy-steroids. In man in Addison's disease we certainly see manifestations of the profound disturbance in protein-carbohydrate metabolism as seen in animals in Addison's disease. They are a counterpart of the opposite end of the spectrum. We see evidence of overactivity of these same substances in Cushing's syndrome. Yet what bothers me terribly is the fact that even with the administration of this new synthetic 11-dehydrocorticosterone, which Dr. Long mentioned, given up to as much as 100 milligrams a day we found precious little in the way of objective evidence of activity. Some reports have come out indicating some increased nitrogen excretion but I think even those have not been as dramatic as one might have expected.

Perhaps the whole answer to this is to be found in a quantitative rather than in any other difference in animals. Perhaps the studies of Martha Vogt may point the way to that.

As you probably all know, in her assay of the blood from the adrenal vein, I think of 10 kg. dogs under nembutal anesthesia, she calculates that approximately 250 cc. of a good commercial extract is elaborated in a day, and it is possible that one of the reasons why we don't see more dramatic effects in man as they are seen in small animals of this type may be purely the quantitative problem.

Finally, I do think that I should like to share Dr. Long's feeling that while tremendous advances have been made in our understanding of the adrenal cortex, there are still some questions which call for solution. I should once more like to express my appreciation to Dr. Long.

DR. LOUIS J. SOFFER: I recall in 1928, or 1930, when it was originally pointed out that the adrenal cortex represented a storehouse for considerable quantities of ascorbic acid. Those of us who are interested in the experimental and clinical study of the cortical insufficiency all thought essentially in the same terms, that it would be worth while seeing the effect of the use of large amounts of ascorbic acid in the treatment of the bilateral adrenalectomized animal and in patients with Addison's disease. You probably know that the results were entirely negative, that the administration of ascorbic acid to the adrenalectomized animal in no way supplements the effect of whole adrenal extract, so if ascorbic acid plays any role in the manufacture of adrenal cortical extract such role can be played only in the presence of intact adrenals. Apparently no other organ in the body is capable of exerting that function.

I was particularly intrigued with the studies of Dr. Long and Dr. Sayers on the effect of epinephrine on anterior pituitary stimulation.

The history of epinephrine too is a very interesting one. When Dr. Abel succeeded in crystallizing epinephrine in the early nineteen hundreds, a good deal of investigative attention was concentrated on the study of the pharmacology and significance of epinephrine. For two decades or more all investigative work was conducted with epinephrine and we really did not think so much in terms of the possibility of other hormone secretions on the part of the adrenal. Finally, when it was realized that the epinephrine by no means represented the only hormone elaborated by the adrenal and attention concentrated on other hormones secreted by the adrenal cortex, I think interest was lost sight of in relation to epinephrine, and this work of Dr. Long represents an awakening of the possible significance of epinephrine.

The fact that epinephrine can be injected and can stimulate the anterior pituitary with the formation of adrenotrophic factor is an important one. In our own laboratory, along somewhat similar lines, we found the injection of epinephrine into intact animals resulted in the secretion of relatively large amounts of thyrotrophic factor and these large amounts are formed in the intact animal, formed in the thyroidectomized animal and formed in the adrenalectomized animal. Curiously enough, in the intact animal the injection of epinephrine eventually loses its effect because of the development of inhibitory mechanism.

On further investigation it was found this inhibitory mechanism is probably related to the adrenal cortex because the inhibitory mechanism does not develop in the adrenalectomized animal, and is promptly manifested again in the event of the injection of whole adrenal cortical extracts. So we see the pendulum swinging back again and epinephrine is beginning to assume a much more important role in adrenal cortical physiology than we had originally suspected or anticipated.

It may be the epinephrine and the sympathetic nervous system act as a trigger mechanism which sets off complete byplay of pituitary function which stimulates the adrenal. Of course if we assume that epinephrine is capable of stimulating the anterior pituitary with the elaboration of adrenotrophic and thyrotrophic factor, it sheds a new light on the carbohydrate function of epinephrine and no longer can we think of it in terms of glycolytic effect but think of it in the larger sense in which it has an extensive effect on the carbohydrate metabolism related in part to the stimulation of the pituitary with the formation of adrenotrophic factor and the effect on the carbohydrate-protein metabolism, and the decrease in the peripheral utilization of carbohydrate.

I agree too with Dr. Long and Dr. Loeb that we are really entering into a new era in endocrine physiology, in endocrine biochemistry, and to those of us who are interested in adreno-cortical physiology, there are many problems which are yet to be solved.

DR. I. ARTHUR MIRSKY: The third discussor usually feels very insignificant, very definitely out of place, because he has to anticipate what the first two are going to say. That is rather difficult on a precise subject of this sort.

Interestingly enough, I did find an aspect which I thought perhaps nobody might mention. I was fascinated to note, like Claude Bernard,

Cannon and other real students of biology, Dr. Long has drawn our attention to the need for viewing a particular problem not from a very precise point of view but from the point of view of the total organism. His data and deductions lead directly to the consideration of the mechanism whereby the organism maintains a constant in terms of Claude Bernard's "milieu interieur" or homeostasis. He has shown us how the adrenal cortex and its products play an essential role in physiologic integrations and demonstrated the manner in which they are affected by disease processes, and how disease processes are affected by them.

It has been known for some time that the pituitary has a dual function in protein metabolism. Studies from our laboratories suggested that the anabolic aspect of pituitary function was due to pancreatrophic effect, a conclusion with which Young and more recently Ogilvie are in accord. However, it was the studies of Long and his group which gave us an understanding and explanation of the catabolic effects of the pituitary, that is, the effect through the adrenal cortex. The recent studies of Cori on the inhibition of the isolated system hexokinase by pituitary extracts opened up a road which may lead us to understand exactly how and where, not only the pituitary but also the adrenal rather may have its effect.

Since corticosterone stimulates the catabolism of protein, that is, stimulates proteolysis, then it may be anticipated that this steroid may actually play some role in intracellular proteolytic enzyme action. The continuation of studies on the effect of purified hormones in specific enzyme systems will undoubtedly enable us to understand sooner those phenomena that we call clinical endocrinopathies.

What have Dr. Long's studies got to do with diabetes? It is almost repetitious for me to point out that his observations and data on the effect of corticosteroids give us the mechanism of, or at least some indications of the mechanisms which are responsible for the increased protein nitrogen excretion which occurs in diabetes. The fact that any stress situation induces increased corticosteroid secretion and consequent increase in protein catabolism makes it easier to understand the fact that the diabetic patient so readily becomes worse at almost the slightest physical or even emotional disturbance; irrespective whether the insult to the diabetic patient produces the effect by the sympathetic nervous system, or through the endocrine system or acts on the diencephalon, there is no question but that it induces increased adreno-

corticotrophic secretion and a consequent increase in adrenal cortical activity, which in turn will induce an increase in catabolism and a state which has many of the characteristics of diabetes. In the diabetic that will produce an aggravation of the existing symptoms and greater needs for insulin, which we would call exacerbation of diabetes or insulin resistance.

In a recent study we demonstrated that emotional disturbances induce hyperglycemia only in diabetic subjects, though glycosuria can be induced even in normal subjects. The work of Selye and of Long help us understand why this emotional disturbance can produce an exacerbation of diabetes in the diabetic subject, since only if homeostasis is sufficiently disturbed will we see the effect of emotional factors acting via the adrenal and pituitary on protein and carbohydrate metabolism.

I may belabor the point but I am anxious to emphasize the importance of Dr. Long's paper in giving us a better understanding of the exacerbation which occurs in the emotionally and organically disturbed diabetic, or even of the fluctuations observed in the so-called juvenile diabetic which makes his treatment so difficult.

Finally, I wish to draw your attention to another clinical phenomenon which is given some explanation. The diabetic's susceptibility to infection and his lack of resistance in general is well known with regard to disturbance. Yet nobody has been able to demonstrate why this should be the case. The studies on lympholysis, so well discussed tonight, give us an inkling of what may be happening. It is quite possible that derangement in cortical function and consequent exhaustion of the lympholytic mechanism may be the basis of the decreased resistance of the diabetic. This gains credence from the work of McCullough who observed loss in blood proteins in patients suffering from diabetes, and especially in the light of Dr. Long's observations. There is no question that the data presented tonight, as other discussers pointed out, suggested innumerable problems to be studied.

I did not hear anybody ask Dr. Long any questions, and in spite of the fact that my voice is failing I shall ask a few.

He has pointed out in the guinea pig with intact adrenals the ascorbic acid content falls under stress or the epinephrine situation, and that the ascorbic acid takes a longer time to return in the guinea pig because it cannot synthesize ascorbic acid and must get it by ingestion. Man too

cannot synthesize ascorbic acid, so the question arises: what happens in the individual exposed to stress, not to Addison's but the individual exposed to stress and presumably suffering from adrenal ascorbic acid insufficiency, will he require ascorbic acid administration?

The next question I should like to ask is, what is Dr. Long's impression as to the adrenal cholesterol and ascorbic acid content in experimental diabetes? I shall not ask him in human diabetes.

DR. LONG: Well, I think I got off very lightly. I was wondering what was going to happen when I saw the team that was lined up to discuss the paper. They have been very kind indeed and all I can say is that Dr. Mirsky spoiled the beautiful friendship growing up between us by asking questions, particularly such difficult ones to answer.

In regard to the relationship of ascorbic acid and the adrenal to stress in man, as to whether a situation could be visualized in which as a result of continued stress there would be a reduction of the adrenal ascorbic acid to a point at which the function of the adrenal is interfered with, that in itself is a question which I cannot give you an answer to. It is now possible to say only one thing and that is I think it has been fairly well established, certainly following burns in man, that the requirement of the whole organism for ascorbic acid is very greatly increased. There are, many of you know, reports of the ingestion of a half or one gram of ascorbic acid a day in these circumstances without practically any of it appearing in the urine. That is not to say all is being used by the adrenal. It would be very difficult to say exactly how much the adrenal is using. All I can say is if it can be shown that ascorbic acid is definitely and essentially concerned with the elaboration of cortical secretion, the possibility does exist in species in whom there is inability to synthesize ascorbic acid to form a secretion adrenal insufficiency might occur if the condition were pushed to a point where the gland was entirely deprived of vitamin. I don't know of any work which has been done on this point.

I can only say we have made an approach to the problem. It is far from complete at the moment. This was done to find out in the guinea pig in which scurvy is produced, as to what its reactions are to many of these situations. The study has not gone forward enough yet but it can be, I think, said there appears in this vitamin deficiency in the guinea pig in contrast to other vitamin deficiencies a specific relationship between the hypertrophy of the adrenal which occurs and the lack of the

vitamin. This much I do know, that the hypertrophy of the adrenal is not an inanition phenomenon as in thiamine deficiency. It appears to be definitely related to lack of vitamin. Obviously one can go on from that point. I am sorry we have not gone on to give you a very good answer to that question.

Strangely enough, and I am sure Dr. Mirsky will think it rather strange, we have never determined the ascorbic acid and cholesterol content in an experimental diabetes. Perhaps now that Dr. Mirsky has raised the point he ought to do the experiment.

I thank you all very much for listening to me so kindly and thank the New York Diabetes Association for asking me to speak this evening.

CHAIRMAN ROSENTHAL: I am sure we are all looking forward next year to learning what the content of cholesterol and ascorbic acid is in the adrenal in diabetes.

THE DIAGNOSIS AND TREATMENT OF CONGENITAL CYANOTIC HEART DISEASE*

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GENERALIZED cyanosis is a sign of the presence in the arterial blood of sufficient reduced hemoglobin to impart a dusky color to the skin and mucous membranes. It is always due either to a return flow of inadequately oxygenated blood from the lungs, or to mixing of the venous and arterial streams within the heart. Since both of these conditions are present throughout fetal life, it follows that the normal fetus is always cyanotic. In the fetus partially oxygenated blood from the inferior vena cava mixes with pure venous blood from the superior vena cava in the right auricle, from there it passes either into the right ventricle, or through the foramen ovale and left auricle, into the left ventricle. The ventricular blood flowing outward through the aorta and that flowing through the pulmonary artery is in both cases mixed venous and arterial, and since the two streams join almost immediately at the junction of the ductus arteriosus with the aorta, there is, in effect, no difference between them. It is not surprising, therefore, to find that developmental abnormalities in the separation of the right heart chambers from the left may offer no serious handicap to fetal development. They affect the child adversely for the first time after birth and the establishment of pulmonary respiration, and then only if the defect is such that a large proportion of the blood which enters the heart can flow out through the aorta without having first passed through the lungs.

Separation of the heart chambers normally occurs early in fetal life by the upward growth of the interventricular septum to join the septum formed by longitudinal division of the primitive truncus arteriosus into two vessels of equal size, the aorta and the pulmonary artery. If this

* From the surgical services of the Presbyterian and Babies Hospitals, and the Department of Surgery, College of Physicians and Surgeons.

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division is unequal, the septum cannot become complete since the base of the larger artery will straddle it. If the larger artery is the pulmonary, blood from both ventricles will pass into the lungs. but the blood which passes out through the aorta will be entirely arterial and no cyanosis will result. If, on the other hand, the aorta is the larger, blood from both ventricles will pass into the systemic circulation, resulting in cyanosis. Cyanosis will also result if the ventricular septum develops so poorly that a large defect remains which permits free ventricular mixing, even though the division of the truncus arteriosus has taken place normally.

These are the most frequent causes of cyanosis due to cardiac mal-development, but they are by no means the only possibilities. The inter-auricular septum normally remains open, through the foramen ovale, until birth. The change in pressures which then occur as a result of the sudden opening of the pulmonary vascular bed normally cause functional closure, but if there is any obstruction to the flow through the right heart, venous blood may continue flow from the right auricle into the left with a resulting mixture of venous and arterial blood in the left ventricle and aorta. Finally, a variety of bizarre abnormalities of the great vessels, especially the pulmonary veins and vena cava, may result in shunting of venous blood into the arterial circulation.

It is not the purpose of this discussion to describe or enumerate all of the abnormalities which may result in cyanosis, but rather to call attention to the features common to those which, as a result of the recent work of Blalock and Taussig, can be helped in some measure by the establishment of a compensatory shunt by operation. If cyanosis is the result of free mixing of venous and arterial blood in the heart, there is at present no compensatory circulatory adjustment which the victim of such an anomaly can make, and none which can be created for him by operation. If, however, the cyanosis is influenced by an obstruction to the flow of blood into the lungs through normal channels, development of a collateral flow may do much to offset it.

Three types of collateral may occur in these patients. The first results from the fact that blood normally enters the lungs not only through the pulmonary artery but also through the bronchial arteries. When the former channel is greatly restricted the latter dilates, sometimes to a remarkable degree. The lung hilus may then be the site of a mass of small tortuous vessels, originating from the aorta, through

which enough blood can pass to maintain life even when the pulmonary arterial channel is virtually completely blocked. The second form of collateral is less effectual, but is usually present to some degree, and, like the first, probably increases as the patient grows older. This consists in the development of new channels, both venous and arterial, which cross from the systemic circulation to the lung through the development of adhesions between the mediastinum and chest wall and the lung. The third and most effective collateral will result if the ductus arteriosus remains patent. This vessel, which in fetal life carries blood from the pulmonary artery to the aorta, allows blood to pass in the opposite direction when it fails to close at birth. Depending on its size, a more or less large proportion of the blood passing out through the aorta will pass back into the lungs and this may act as a very effective collateral if there is a block in the pulmonary artery. If, then, this channel tends to close, or fails to increase in size as the child grows, compensation will become progressively worse, cyanosis will deepen, and ultimately death may follow.

Knowledge of the existence of this type of collateral is not new, but Taussig¹ was the first to suggest that a collateral of the same type might be produced surgically, and the brilliant work of Blalock² has proved the correctness of her view. By bringing the proximal end of a large vessel originating from the aortic arch, either the innominate, one of the subclavians or one of the carotids to the side or distal end of either pulmonary arterial branch, the surgical equivalent of a large patent ductus can be created. Such a shunt has been used in animals by Eppinger, Burwell and Gross³ to study the effects of ductus patency and was shown by them to divert a large amount of blood into the lung. It is a technically difficult operation to perform and its effectiveness depends on the existence of a pulmonary vessel of sufficient size to permit it, a situation which is not always present. It also may be prevented by anomalies of the aortic arch and great vessels, but when it can be carried out, the effectiveness of the creation of such a new collateral shunt may be dramatic.

How, then, can we distinguish those abnormalities which can be relieved? When the aorta overrides a small, high septal defect and the pulmonary artery is poorly developed, blood entering the right ventricle may leave either through the aorta or through the pulmonary artery. In these cases there is frequently a very narrow and rigid stenosis of the

latter. As a result the right ventricle becomes enlarged and hypertrophied and the systolic pressure developed within it is high even at rest. The amount of blood passing through the stenotic pulmonary artery at rest is, in those children who survive the neonatal period, enough to sustain life, but its proportion to that which passes through the aorta varies with the total amount which enters the heart. Thus any increase in flow will cause a large proportion of blood to flow from the right ventricle into the aorta and cyanosis will increase. Similarly any increase in resistance in the pulmonary circuit will increase the shunt.

These individuals will, then, show a degree of cyanosis at rest which reflects the severity of the pulmonary block. It may or may not be conspicuous. With exertion or with excitement, and especially with crying, the cyanosis rapidly deepens so that the child becomes extremely dyspneic and may even lose consciousness or develop convulsions. There is usually a harsh systolic murmur over the base of the heart, the character and site being variable. On x-ray the heart shows enlargement of the right ventricle, but not much general enlargement, and a concavity in the region of the pulmonary artery. The electrocardiogram shows right axis deviation. This is the combination known as the Tetralogy of Fallot.

With time, compensatory polycythemia develops, increasing the oxygen carrying capacity of the blood, but also increasing its viscosity. This increased viscosity then further slows the flow through the narrowed pulmonary opening and contributes a further element of block, so that a vicious cycle is established. In extreme cases this may result in spontaneous thrombosis, especially in the cerebral vessels. In others acidosis from incomplete oxidation in the tissues or loss of carbon dioxide due to hyperventilation may occur. Similar symptoms and physiologic disturbances will result from other anomalies in which an intracardiac right to left shunt is increased by pulmonary vascular block, though the shape and size of the heart will be different, and the murmur and changes in the electrocardiogram may vary greatly.

When cyanosis is due to mixing without pulmonary block, it may be severe but will vary less. Exertion will cause dyspnea, and exercise will be limited by the ability of the circulation to carry oxygen to the tissues, but an increase in cardiac output will not change the proportion of mixing so extreme evidences of acute oxygen lack will not be evident. Such patients may show great enlargement of the heart, but it

will be less asymmetrical, and the pulmonary arterial shadow will often be prominent. Murmurs may or may not be present, and the electrocardiogram will not as often show right preponderance.

The degree to which these changes are present is extremely variable. When it is extreme, the evidences of pulmonary block are clear, but in individuals less severely affected the distinction is frequently difficult. It is in such cases that studies by the method of intracardiac catheterization developed by Cournand and Ranges⁴ are especially valuable, not only in establishing the nature of the anomaly, but especially in determining whether shunting of peripheral blood into the pulmonary circulation can be expected to alleviate the symptoms.

During the past two years twenty-eight patients have been studied at the Columbia-Presbyterian Medical Center as possible candidates for operation. Of these, 16 have been operated upon, and 12 were rejected, because it was believed that a shunt would not help them. In seven of these intracardiac catheterization studies were done by Doctors Baldwin, Greene and Mathers. A detailed description of the method and analysis of the data is not suitable here. In general, the method consists of introducing a catheter into the right auricle, where pressures are recorded and from which a sample of blood is withdrawn. The catheter is then passed into the right ventricle and, if possible, into the pulmonary artery. In some cases anomalies have permitted it to pass also into the left auricle, pulmonary veins, and left ventricle. Each position is checked fluoroscopically, and pressures and blood samples are taken from each site. Analysis of the data will then give direct information on the pressure relationships of the various chambers and the degree of mixing of arterial and venous blood in each. By using this data in combination with simultaneous determination of oxygen consumption in the lungs, and oxygen content of the arterial blood (obtained from the femoral artery) the peripheral blood flow can be calculated indirectly by the Fick principle. This can then be compared to similar indirect calculation of the pulmonary blood flow by assuming 95 per cent saturation of the pulmonary vein blood. With this information the type of anomaly can be deduced with, we believe, reasonable certainty.

By this method the seven cases which were studied and considered unsuitable for operation were analyzed as follows:

Case 1: An adolescent deaf mute permitted sampling from all four

cardiac chambers, proving the presence of a patent foramen ovale. The right ventricular blood contained more oxygen than the right auricular, but less than the blood in the left ventricle; this, in turn contained less than the left auricular blood. The blood in the peripheral artery was intermediate between that in the right and left ventricles. Thus mixing in the ventricles was present which was the cause of his cyanosis. This conclusion was further confirmed by the fact that his pulmonary blood flow was calculated between one and three times that of his peripheral. It was concluded that no operation would help.

Case 2: A Bermudian colored boy, at first was thought to be a case for operation because x-ray and electrocardiograms indicated a Tetralogy of Fallot. The right ventricular blood contained more oxygen than the auricular, but less than the peripheral blood, showing a left to right shunt through a ventricular septal defect, with the aorta receiving most of its blood from the left ventricle. Furthermore the pulmonary arterial blood at the point of bifurcation was identical with the aortic, demonstrating the presence of a compensating patent ductus arteriosus. The pulmonary blood flow was almost identical with the peripheral, proving that the shunt provided by the ductus was adequate in volume, so that no further advantage would be gained by producing a new shunt surgically.

Case 3: A child of missionary parents whose cyanosis became pronounced during their stay at a mission high in the hills of India. Her pulmonary arterial blood was almost identical in oxygen content with her peripheral, though the right ventricular blood was lower. Thus both great vessels received blood from both ventricles, indicating a large defect, an interpretation confirmed by the finding of a pulmonary blood flow over twice that of the peripheral.

Case 4: A deeply cyanotic child whose mother, a nurse, had set her heart on operative "cure." Pulmonary arterial blood was not obtained, but the finding of a pulmonary flow 25 per cent greater than her peripheral made it clear that there was no obstructive element, the cyanosis being due to a large septal defect.

Case 5: A little boy who showed only transient cyanosis. His pulmonary blood flow was over three times his peripheral, demonstrating a small septal defect with predominantly left to right flow and no obstruction.

Case 6: Another little boy with similar, though less marked, findings.

TABULAR SUMMARY

	Improved Dra- matic	Mod- erate	Post- Oper- ative	Died	Total	Per Cent Mor- tality
Right Innominate-Pulmonary: End-to-Side	1	1			2	
Right Innominate-Pulmonary: End-to-End				1	1	
Right Subclavian-Pulmonary: End-to-Side	2	2	1	1	6	
Right Subclavian-Pulmonary: End-to-End		1			1	
Left Subclavian-Pulmonary: End-to-Side	1	.			1	
Left Subclavian-Pulmonary: End-to-End	1				1	
Total Anastomoses Completed	5	4	1	2	12	17%
Anastomosis Not Completed		.	1	3	4	75%
Total	5	4	2	5	16	31%

Case 7: A boy who showed an increase in oxygen content of the right auricle over that in the vena cava, demonstrating the presence of an auricular septal defect with the left to right shunt, and a higher pulmonary than peripheral flow. It is possible that the auricular defect acts in this case in a compensatory manner, but it could not do so if there were any appreciable block in the pulmonary artery.

Of the sixteen cases operated upon, only two were studied by intracardiac catheterization because we prefer not to use the method in very small children. In both instances the diagnosis of pulmonary stenosis was confirmed at operation. The remaining operative cases were selected because the findings on physical examination, x-ray and electrocardiography made the diagnosis of interference with pulmonary flow reasonably certain. All of them were severely handicapped, some more than others. The diagnosis was confirmed at operation or autopsy in all but two. One of these, who died on the operating table, showed at autopsy a rudimentary right ventricle with an almost obliterated pulmonary artery. The blood stream passed from the right auricle through a large defect into the left and thence through the ventricle into the aorta. Practically all of his pulmonary flow entered the lung through collaterals of the bronchial artery, and when these were divided in exposing the pulmonary artery for anastomosis, acute anoxemia and death occurred. The other showed a pulmonary artery of normal size, and

though an anastomosis was successfully accomplished it is doubtful whether he will show much improvement.

Five patients died, an over-all mortality of 31 per cent, two on the operating table and three postoperatively. In two of these the anastomosis was successfully accomplished and death was due to errors in postoperative care. In the other three, including the two who died on the table, death was presumably due to anoxia which resulted from dividing collateral to the lung without providing the more effective anastomotic collateral. In the remaining thirteen cases, anastomoses were accomplished in all but one. This boy proved to have an anomaly of the great vessels of the aorta such that no large peripheral artery could be found for anastomosis. He has recovered from operation and it is possible that a second attempt on the opposite side may prove successful.

The type of anastomosis to be performed cannot always be determined beforehand but must depend in part on the anomalies encountered, in part on the amount of flow it is desired to create. Thus Blalock⁵, in 246 cases, has performed right subclavian to pulmonary, end-to-side in 150, other end-to-side anastomoses in 57, and other procedures in 39, with an over-all mortality of 21 per cent.

In our experience, successful completion of an anastomosis has resulted in dramatic improvement in 5, moderate improvement in 4, the remaining one being too recent to be sure. Those who have been improved dramatically have changed from miserable little things who could hardly walk across a room without having to squat for breath, or who had to be carried, into children who, though limited in exercise tolerance, can lead a fairly normal, if restricted, life. They show little or no clinical cyanosis, their polycythemia is much less, and they have begun to lose the clubbing of fingers and toes. Those in whom improvement was less dramatic were, in general, less restricted to begin with. Their exercise tolerance is better and their cyanosis is less. It must be emphasized, however, that restitution to normal is never accomplished and that the ultimate course remains in doubt. It seems probable that many will ultimately succumb to circulatory failure, as in the case of uncomplicated patent ductus, and the threat of subacute bacterial endocarditis is probably increased by the procedure. These liabilities, together with the uncertainties of diagnosis, the technical difficulties of the procedure and the poor surgical risk that these patients present must

temper our enthusiasm in recommending operation, and restrict its use to those patients whose prognosis is otherwise hopeless; for these, however, it offers real hope in an otherwise desolate outlook.

SUMMARY

The physiologic and anatomic abnormalities which are found in cases of congenital anomalies of the heart associated with cyanosis have been discussed. It has been brought out that in certain cases the establishment by operation of a shunt between the peripheral and pulmonary circulation, as demonstrated by Taussig and Blalock, may do much to relieve the symptoms. The problem of selection of those cases which can be helped by operation is explored and the usefulness of intracardiac catheterization studies is demonstrated by citing seven cases studied by Baldwin and her co-workers in whom it was demonstrated that operation would not be useful. Sixteen cases are reported in which operation was done in an attempt to produce a new collateral shunt, of which some type of anastomosis was accomplished in twelve. The over-all mortality was 31 per cent, and in those in which the anastomosis was accomplished it was 17 per cent. The operation resulted in dramatic improvement in five severely handicapped children, in four the improvement was moderate. The risks and limitations of the procedure are brought out, as well as its great usefulness in selected cases.

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STUDIES IN NEW ANTICONVULSANTS*

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INTRODUCTION

APPROXIMATELY ten years ago, while working with Dr. Tracy J. Putnam in Boston, the conclusion was reached that all of the physiological and biochemical studies which had been made up to that time on patients with seizures, had not brought us to the solution of the problem of the causation of seizures; nor had these studies resulted in any significant advances in our methods of controlling or reducing the number of seizures in patients with symptomatic or idiopathic epilepsy. In fact, there had been no progress in the medical treatment of patients with seizures since 1912 when Hauptmann introduced the use of phenobarbital. It was, therefore, decided to approach the problem from a different angle by making a systematic study of the anticonvulsant activity of a large number of chemical compounds.

Methods: The method of testing the anticonvulsant action of a compound which was in general use at that time, namely, protection against convulsant drugs, was cumbersome, costly, and unreliable. In addition, it was thought that the convulsions resulting from electrical stimulation of the cerebral cortex were physiologically more closely related to the spontaneous convulsions in humans than those produced by convulsant drugs. An apparatus¹ was devised by which a direct current could be passed through the head, between two electrodes, one of which was placed on top of the skull and the other in the animal's mouth. Cats were selected for test subjects because of their availability and the convenience in handling. It was shown that the amount of current, as measured in milliamperes, necessary to produce a convulsion in a given animal, was remarkably constant on repeated testing during one day or on different days. It was also shown that drugs, such as phenobarbital or bromides, which were known to reduce the frequency of seizures

* From the Division of Neuropsychiatry, Montefiore Hospital and Department of Neurology, College of Physicians and Surgeons, Columbia University. Given November 12, 1946 before the Section of Neurology and Psychiatry of The New York Academy of Medicine.

in many patients with epilepsy, were effective in raising the convulsive threshold to electrical stimulation in cats. Conversely, it was also shown that a procedure which increased the frequency of seizures in epileptics, such as excessive hydration by the exhibition of pitressin parenterally and water by mouth, caused a lowering of the threshold to the electrical stimulation in the animals.

A number of chemical compounds were selected for testing on the basis of the similarity of their structural formulae to that of known anticonvulsants. Various pharmaceutical manufacturers also were invited to submit for testing all compounds which could conceivably have an anticonvulsant action.

By this method, it was possible to make a preliminary screening² of a large number of compounds (over 700). A few of the compounds which were found to have a high degree of protective action against electrically induced convulsions, were selected for further studies in animals to determine whether they could be considered suitable for clinical use in patients subject to convulsive seizures. These studies included chronic tests in animals to determine whether continued daily administration of the compound would result in a maintenance of a high level of resistance to electrically induced convulsions and administration of the compound to various animals (mice, cats and dogs) for periods of several months to determine whether toxic changes would result from long continued administration.

Results: Approximately 10 per cent of the 700 compounds were found to produce a significant elevation of the convulsive threshold in the acute experiments (Table I). While it has not been possible to determine the exact chemical radical or radicals which are effective in raising the convulsive threshold, the effective compounds fell into six main groups: barbiturates, benzoxazoles, hydantoins, ketones, oxazolidinediones, and phenyl compounds with sulphur.

Unfortunately the laborious and time consuming nature of the preliminary testings and the toxic properties and unpalatable taste of some of the compounds have made it impossible to carry out clinical tests. up to the present time, on more than a few of these compounds, and in only one, 5,5 diphenylhydantoin, has this clinical trial been extensive. This is due, in part, to the fact that the results obtained with this compound, which was one of the first to receive a clinical trial, were so superior to the results obtained with previous forms of medical treat-

TABLE I

LIST OF COMPOUNDS HAVING A HIGH DEGREE OF ANTICONVULSANT ACTIVITY IN ANIMALS

BARBITURATES		
5-n-Butyl-5-phenylbarbiturate, sodium	5-Methyl-5-(1-naphthyl)-hydantoin	Sodium-5-phenyl-5-(tetrahydropyrane-4)hydantoinate
Ethyl i-amyl barbital	5-Methyl-5-phenoxy-methylhydantoin	Sodium 5-(n-propoxymethyl)-5-phenylhydantoinate
5-Phenyl-5-ethyl barbital	5-Methyl-5-phenylhydantoin	α -Tetralonespirohydantoin
5-n-Propyl-5-n-butylthiomethyl barbituric acid	3-Methyl-5-n-propoxymethyl-5-phenylhydantoin	
Sodium cyclopentenyl allyl barbituric acid	3-Methyl-5-i-propoxymethyl-5-phenylhydantoin	
BENZOXAZOLIS		
1-Benzylbenzoxazole	5-(1-Naphthyl)-5-n-propylhydantoin	KETONES
1-Methylbenzoxazole	5-Phenyl-5-(benzylmercapto-methyl) hydantoin	Acetophenone
2-(α -n-Propyl- β -phenoxy)-butylbenzoxazole	5-Phenyl-5-i-butylhydantoin	Acetophenone oxime
HYDANTOINS		
5-i-Amoxymethyl-5-phenylhydantoin	5-Phenyl-5-n-butylmercapto-methylhydantoin	Acetylbenzoyl
5-(n-Butoxymethyl)-5-phenylhydantoin	5-Phenyl-5-i-butylsulfonyl-methylhydantoin	α -Benzoin oxime
5-(i-Butoxymethyl)-5-phenylhydantoin	5-Phenyl-5-cyclohexylmercapto-methylhydantoin	Benzoylacetone
5-(t-Butoxymethyl)-5-phenylhydantoin	5-Phenyl-5-(1, 2-dimethylpropoxy-methyl)hydantoin	Benzyl carbamate
5-n-Butyl-5-(1-naphthyl)-hydantoin	5-Phenyl-5-ethylmercapto-methylhydantoin	Benzy methyl ketone
5-i-Butyl-5-(1-naphthyl)hydantoin	5-Phenyl-5-methylsulfonyl-methylhydantoin	Benzyl methyl ketone oxime
5-Cyclobutyl-5-cyclohexylhydantoin	5-Phenyl-5-methylmercapto-methylhydantoin	Dibenzyl ketone
5-Cyclobutyl-5-phenylhydantoin	5-Phenyl-5-n-propylhydantoin	Diethyl ketone
5,5-Diphenylhydantoin	5-Phenyl-5-i-propylhydantoin	β -Dimethylaminoethyl-2-naphthyl ketone hydrochloride hydrate
5,5-Di(α -thienyl)-hydantoin	5-Phenyl-5-n-propylmercapto-methylhydantoin	2-Furyl phenyl ketone
5-Ethyl-5-(1-naphthyl)hydantoin	5-Phenyl-5-i-propylhydantoin	p-Hydroxyacetophenone
5-Ethyl-5-(2-naphthyl)hydantoin	5-Phenyl-5-n-propylmercapto-methylhydantoin	Paraldehyde
5-(1-ethylpropoxymethyl)-5-phenylhydantoin	5-i-Propoxymethyl-5-phenylhydantoin	Phenyl n-amyl ketone
5-Methoxymethyl-5-phenylhydantoin	5-n-Propyl-5-(1-naphthyl)hydantoin	Phenyl n-butyl ketone
5-(2-Methyl-butoxymethyl)-5-phenylhydantoin	Sodium 5-ethyl-5-i-amylhydantoinate	Phenyl propyl ketone
3-Methyl-5-ethoxymethyl-5-phenylhydantoin	Sodium 5-phenyl-5-phenthyl hydantoinate	Propiophenone
		i-Valerophenone
		OXAZOLIDINEDIONES
		5,5-Diphenyl-2,4-oxazolidinedione
		5,5-Di-n-propyl-2,4-oxazolidinedione calcium
		PHENYL COMPOUNDS WITH SULFUR
		α -(o-Aminobenzenesulfonamido)-pyridine
		2,4-Diaminothiazolyl phenyl sulfone
		Ethyl phenyl sulfone
		Ethyl phenyl sulfoxide
		Ethyl phenyl sulfide
		Propyl phenyl sulfoxide
		i-Propyl phenyl sulfoxide

ment, that it has been the custom to administer other compounds only to those patients whose seizures were not relieved by 5,5 diphenylhydantoin. This procedure does not give a true index of the clinical anticonvulsant activity of the other compounds but rather measures their effectivity in patients who have been refractive to 5,5 diphenylhydantoin and also to previous forms of therapy, including phenobarbital, mebaral and the bromides. This procedure was considered justifiable, however, since the object of the study was to find the most efficient anticonvulsant, and not merely a substitute for a previously established anticonvulsant. The study is still in progress and new compounds are being tested as soon as the chronic toxicity studies indicate that they are suitable and pharmacological methods of large scale production are available. This report will deal with only those compounds which have been given a fairly extensive trial to date.

*5,5 Diphenylhydantoin**: The results obtained in the treatment of 200 patients with sodium 5,5 diphenylhydantoinate (dilantin sodium, phenytoin sodium) were reported to the American Medical Association at their meeting in 1938 by one of the authors and Dr. Tracy J. Putnam.³ Further experience with this compound in a large series, was reported in 1940⁴ and 1942⁵. The efficacy of sodium 5,5 diphenylhydantoinate in preventing convulsive seizures in humans, has been confirmed by many observers⁶ and it is now generally recognized that it is the most effective agent for the prevention of grand mal and psychomotor seizures that is available at the present time.

In spite of the excellent results which have been obtained with sodium 5,5 diphenylhydantoinate in grand mal and psychomotor attacks, it does not have any appreciable effect on petit mal or prevent the occurrence of grand mal or psychomotor seizures in all patients. In addition, the administration of an effective dose is not possible in some instances due to the development of untoward side reactions (ataxia, nystagmus, gastric distress, skin rashes and hypertrophy of the gums).

*5 Methyl, 5 Phenyl Hydantoin**: 5 methyl, 5 phenyl hydantoin was administered to forty-one patients for periods ranging from five days to one year. All of these patients had previously been treated with various anticonvulsant drugs, including 5,5 diphenylhydantoin, phenobarbital and mebaral, either alone or in combination and they had not been re-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE II

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF
5-METHYL-5-PHENYLHYDANTOIN
TO 41 PATIENTS WITH CONVULSIVE SEIZURES

	<i>Number of Patients</i>
Entirely Controlled	9
Reduced in Frequency	10
Increased in Frequency	1
Frequency Unchanged	6
Insufficient Observation	15*

* In the majority of these patients, treatment was discontinued after a few days because of skin rash.

lieved of their seizures by these forms of medication.

This compound was administered to twenty-six of the forty-one patients for a sufficiently long period to evaluate its anticonvulsive activity. The attacks were entirely controlled in nine (35 per cent), reduced in frequency in ten (38 per cent), unchanged in six (23 per cent), and increased in frequency in one (4 per cent) (Table II). In the remaining fifteen patients, the anticonvulsant activity of the compound could not be evaluated because of the occurrence of an allergic dermatitis in fourteen and gastrointestinal symptoms in one patient.

With regard to the type of seizures, the beneficial effect of this compound was greatest when the seizures were of the grand mal or psychomotor type. The compound was administered to only a few patients with petit mal seizures and in one of these, the attacks were increased in frequency.

A skin rash developed in fourteen of the forty-one patients (34 per cent). In twelve of the fourteen patients with this reaction, the rash was of a scarlatiniform or morbilliform nature and appeared five to ten days after starting the treatment. The rash recurred with readministration of the drug in all but one case. In two patients the rash took the form of an exfoliative dermatitis which appeared after about ten days of use of the drug. In one of these patients there was also a severe eosinophilic reaction in the blood with displacement of the red cells in the bone marrow and a severe anemia. There were no fatalities and no

TABLE III
CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF
5-*i*-PROPOXYMETHYL-5-PHENYLHYDANTOIN
TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	<i>Number of Patients</i>
Transient Reduction of Frequency of Seizures.....	5
Frequency Unchanged	20

other serious side reactions encountered with the use of the drug in doses varying from 0.4 to 1.0 gram daily, with the exception of a mild degree of gastric distress in three patients. In particular, there was no hypnotic action, ataxia or gingival hyperplasia.

The results obtained with the administration of 5 methyl, 5 phenyl hydantoin, indicate that it has an anticonvulsant activity equal, or superior to that of 5,5 diphenylhydantoin or phenobarbital since the seizures were either controlled or reduced in frequency in nineteen of the twenty-six patients (73 per cent), who had previously been treated with the latter drugs.

It is evident that this compound merits further trial, particularly if it can be prepared in a form which can be administered without so high an incidence of allergic skin reactions.

*5-Isopropoxymethyl-5-phenylhydantoin**: This compound⁷ was administered for periods varying from one to three months' duration to twenty-five patients (Table III) whose seizures were not controlled by phenobarbital and 5,5 diphenylhydantoin. The administration of this compound did not result in any significant change in the frequency of seizures, either when it was administered alone or in combination with their previous forms of therapy. There was a transient reduction in the frequency of the attacks in a few patients but this improvement was not maintained. There were no toxic side effects noted from the administration of this compound in dosages varying from 0.4 to 2.0 grams daily in this small number of patients. Hypertrophy of the gums, which was present in one patient previously receiving 5,5 diphenylhydantoin, receded while the 5-isopropoxymethyl-5-phenylhydantoin was being administered.

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE IV
CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF
5,5 DIPHENYLENE HYDANTOIN
TO 43 PATIENTS WITH CONVULSIVE SEIZURES

	Number of Patients
Entirely Controlled	5
Reduced in Frequency	7
Frequency Unchanged	24
Insufficient Observation	7

*5,5 Diphenylene Hydantoin**: 5,5 diphenylene hydantoin (diphenylene diimide; diphenylene glycolyl urea) was given to forty-three patients with convulsive seizures for a period varying from two weeks to thirty-five months (average six months). The anticonvulsant activity could be evaluated in thirty-six of these patients. In the remaining seven patients it was not possible to estimate accurately the anticonvulsant effect of the compound either because prolonged administration was prevented by the appearance of a toxic skin reaction or because follow-up data were inadequate or unreliable.

In thirty-one of the thirty-six patients, seizures had not been controlled by various other forms of therapy and in five, the 5,5 diphenylene hydantoin was the first form of therapy. The results obtained in these five patients, plus the thirty-one patients refractory to other forms of therapy, are shown in Table IV.

In the thirty-one patients who had been treated with phenobarbital and dilantin, the attacks were entirely controlled in three (8 per cent), greatly reduced in frequency in five (14 per cent), and not significantly affected in twenty-three (78 per cent). The reduction in frequency of attacks, when present, was in grand mal or psychomotor equivalent attacks. No effect was noted in the frequency of petit mal attacks in the three patients in this group who were subject to this type of attack.

In the five patients who had not received any adequate treatment previously, there was complete remission of attacks in two (both of whom had frequent petit mal and grand mal attacks) and great reduction of the frequency in an additional two. In the remaining case, there

* The toxicity studies on this compound were made in the laboratories of The Wm. S. Merrell Company. We are greatly indebted to them for supplying us with the drug used in this study.

was a temporary remission in the attacks with later recurrence at their previous frequency. All five of these patients had frequent attacks and were treated with 5,5 diphenylene hydantoin for seven months or more.

The dosage administered varied between 0.4 and 2.3 grams daily. The effects of excessive dosage were similar to those seen with mild dilantin intoxication: ataxia, nystagmus, diplopia and dysarthria, without drowsiness. The majority of adults were able to take 1.7 gm. daily (the usual maximum dose) without developing these symptoms, although an occasional patient could not. One patient took 2.3 gm. daily regularly for months without ill effect.

Seven patients of the forty-three (16 per cent) developed an allergic dermatitis while taking 5,5 diphenylene hydantoin and in one patient this diagnosis was made but was later considered doubtful. The time of onset of the rash varied from eight to twenty-one days after the first dose (average ten days). The rash was usually morbilliform, occasionally scarlatiniform, and was often accompanied by fever, headache, malaise, nausea and vomiting. No patient developed exfoliative dermatitis. In four of the seven patients, administration of 5,5 diphenylene hydantoin was resumed after the rash had disappeared. Three of these four patients were then able to continue taking 5,5 diphenylene hydantoin regularly and in adequate dosage without further difficulty, while in the other patient there was prompt reappearance of toxic symptoms necessitating withdrawal of the drug again. No patients died from any cause while taking 5,5 diphenylene hydantoin.

From our limited experience with this compound, it was concluded that it had a definite anticonvulsant activity but that it was not clearly superior to phenobarbital and 5,5 diphenyl hydantoin in refractory cases. In order to determine better its anticonvulsant efficacy in comparison to phenobarbital or 5,5 diphenyl hydantoin, it should be tested in a larger group of patients not previously shown to be refractory to those drugs. The compound has no hypnotic action and the toxic side effects of the drug are not serious although the incidence of allergic dermatitis is relatively high.

*Ethyl Phenyl Sulfone**. Twenty-five patients were given ethyl phenyl sulfone⁸ for periods varying from one week to seven months. All patients had been previously treated with adequate doses of pheno-

* The toxicity studies on this compound were made in the laboratories of Parke, Davis & Company. We are greatly indebted to them for supplying us with the drug used in this study.

TABLE V

CLINICAL RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF
ETHYL PHENYL SULFONE
TO 25 PATIENTS WITH CONVULSIVE SEIZURES

	<i>Number of Patients</i>
Frequency Reduced	4
Frequency Unchanged	21

barbital or 5,5 diphenylhydantoin alone, or in combination. The effects of administration of this compound are shown in Table V. There was a reduction in the frequency of attacks in four, and no appreciable change in frequency in twenty-one. Complete relief from attacks was not obtained in any of the twenty-five patients, although a combination of ethyl phenyl sulfone, and 5,5 diphenylhydantoin or phenobarbital was tried in seventeen of the twenty-five patients.

There were no significant toxic side effects from the administration of ethyl phenyl sulfone in the dosages used, i.e., 0.6 to 1.6 grams daily. In three patients there was a slight degree of ataxia when taking over 1.0 gram daily.

SUMMARY

Over 700 chemical compounds have been tested for anticonvulsant activity in animals. Approximately 10 per cent of these demonstrated a high degree of anticonvulsant activity by these tests.

Only a few of these compounds have been given a clinical trial in patients with convulsive seizures. One of these, 5,5 diphenylhydantoin, has proved to be the most effective anticonvulsant yet discovered. None of the remaining compounds which has been given a clinical trial has proved superior to 5,5 diphenylhydantoin, with the possible exception of 5 methyl, 5 phenylhydantoin. This latter compound is not as yet suitable for general use on account of its toxic side effects.

Additional chemical compounds are being tested for their anticonvulsant activity in animals, and a clinical study of a larger number of those compounds which have an anticonvulsant activity in animals is in progress.

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INTRINSIC ASTHMA *

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IN the beginning all *was* allergy that wheezed, and if the methods peculiar to allergy could not reveal the cause, these methods were deemed faulty. It was recognized, however, that the simple allergic process could be aggravated and continued by secondary infections. Still later, primary infections came to be regarded as the cause of asthma—particularly when patients were found to have no trouble except at the time of a new head cold. They were said to have “bacterial allergy.”

More recently chronic focal infections, as in teeth and sinuses, have been recognized as quite sufficient to explain chronic asthma.

The study of end results has led to the study of the clinical classification of asthmatic patients. The fact that these classifications, made by different workers, are all a little different, and that classifications made by the same worker at different times are also different indicates that no classification is really satisfactory. Within the past year or two, however, it has been possible to develop a simple classification of asthma which has been proved to be of considerable practical value in the clinic. The age of onset appears to be of real importance. On the one hand there are many patients whose asthma begins in childhood or in the teen ages and is evidently related quite closely to changes in season or environment. A careful history shows that the asthma comes and goes in certain places or occurs only at certain times of the year or, more rarely, depends upon the eating of certain foods. Allergy seems to be a satisfactory explanation for the cause of trouble and the diagnosis of this depends upon the history. Skin tests are helpful, but when one finds many positive skin tests with no history to go with them, and when the patient knows well of his or her sensitiveness to cats, for example, but still has no skin test to cat hair extract, one has to recognize that the skin tests have their limitations.

* Abstract of presentation February 6, 1947 at Stated Meeting of The New York Academy of Medicine

The prognosis in this early allergic group is good. A goodly number of these young people have outgrown their asthma entirely, and in the others their freedom from asthma depends upon their success in avoiding the exciting agent or perhaps in being protected against it by desensitization. In this group of simple allergic asthma, the problem is not too difficult and the mechanism is reasonably clear.

"Asthmatic Bronchitis." In some of these young people the asthma occurs only with new colds and one can show quite often that when the family dog or the feather pillows are removed then new colds are no longer accompanied by wheeze. In this way one can show that the disturbance has two factors; the new cold to precipitate the attack and at the same time to lower the threshold to make a slight allergy effective. The elements of infection and of allergy are both present and the treatment here has two objects. One is directed toward the basic allergy, the other toward the prevention of new colds, mostly by trying to improve the general condition of the patient. Vaccines may be helpful.

Vasomotor Rhinitis Leads to Asthma. There is a special group of these young people in which the symptoms are so characteristic and so severe that the group seems to constitute almost a special disease entity. Here are people, mostly women, who in their middle twenties develop a chronic vasomotor rhinitis which this time is severe and persists. It bears no relation whatever to changes in season or in environment, or to food. All skin tests are negative. The symptoms do not respond to treatment. After two or three years a wheeze—asthma—is added to the picture and like the nasal symptoms this wheeze is persistent and soon it becomes severe. A number of these young women have died in an attack of violent asthma and at autopsy have shown the typical sticky plugs which occlude all the bronchi. A report of these special cases is in preparation.

* * * * *

The older group of asthmatics is of great practical importance, and it is more interesting if only because we do not know so much about it. In times past I have called the asthma in these cases "intrinsic," and for the reason that the clinical history shows that whatever the cause of trouble, it is something which the patient carries with him through all seasons and in all places, including the hospital ward. Environmental factors as well as specific foods play no part. One can anticipate, and later show that all skin tests are negative.

The causes of trouble in these intrinsic cases are numerous. "*Bacterial allergy*"—a sensitiveness to some particular organism or to the products of its growth in the body—is a theory easily suggested by the findings in the extrinsic group. Unfortunately, however, bacterial allergy can not be demonstrated by skin tests which ought to show a typical wheal and erythema reaction. It is true that vaccines and toxins will produce red inflammatory reactions appearing in 24 hours, but such reactions are not specific. One can obtain them with similar vaccines and toxins made with the cultures from other sources beside the patient himself.

"*Depletion*" was described by me last year;¹ a broad term which indicated that the asthma was due to a burden of somatic or psychic diseases, or perhaps by both factors together. Selye's² Adaptation Syndrome with the alarm proper, including the shock and counter shock stages, followed by resistance and finally exhaustion, appears to fit fairly well. The point is that treatment of the patient as a whole without too much attention to his asthma has brought good results.

"*Polypoid Sinusitis with Asthma*" has appeared to include a particularly difficult group of patients whose asthma is closely associated with lesions of the nose and sinuses. Further study confirms the early impression that the nasal lesions are part of the picture and not a cause of it. In the first place, more careful examination will show that turgescence of the nasal membrane, or thickening of the sinus linings is almost universal in asthma, and secondly, the end results do not show that patients with more obvious lesions behave any differently in the long run from those whose nose is relatively clear.

Emphysema occurs as a part of every asthmatic attack, but the acute process is reversible. There is, however, a special group of cases whose emphysema is primary. Why or how it develops is quite unknown. The symptoms are much like those of asthma with one interesting exception. In emphysema the nights are good—"emphysema sleeps well." In asthma, however, the nights are bad. The distinction is simple and often useful.

Finally, *Tumors and foreign bodies* must never be forgotten for they, too, can simulate all the symptoms of "asthma."

* * * * *

Such a classification is useful in the clinic, as said. Still, however, it does not reveal the cause of asthma.

My father was a lawyer. He asked me one day, "Don't you ever

cure your patients?"—"If you do, why don't you find out how you did it?" I have been trying ever since to find the answer to that question.

Studies of end results should be helpful. Gross figures for end results in Intrinsic Asthma, arranged according to the age and decade of onset show that 20 per cent of the patients are "cured" and this figure applies roughly to all the age groups. Improved are 24 per cent and unimproved only 8 per cent. Deaths from asthma itself occurred in 13 per cent, but the figure is higher for the younger groups, just as deaths from causes other than asthma are higher for the older groups. These gross figures, however, do not mean too much. Whereas the number of cases is large in the clinical sense, it is still too small for statistical purposes.

Special study of the "cured" cases reveals a number of interesting points.

The reasons for cure, appraised partly by the patient and partly by the family doctor, vary widely. In several cases it was our treatment with vaccines, usually in combination with potassium iodide, together with protective measures, including ephedrine and adrenalin, which started the patient in the right direction. The list, however, includes other statements. Asthma disappeared when divorce was arranged; it cleared when the menopause was finally completed; when the obesity was treated; and then in other cases it was simple directions about decent living which were of great value. The woman was always tired; her diet was poorly arranged; life was hectic; emotions were near the surface; and when these things were cleared, her asthma disappeared. In other patients, and in men more than women, it was the removal of a focus of infection which seemed to do the trick. The extraction of abscessed teeth has, in certain cases, been all that was required to change the patient from a hopeless invalid to a reasonably healthy and useful person.

Sinus operations are always interesting, and the tabulation shows that in a few cases sinus surgery was in fact followed by a "cure" (in quotation marks). On the other hand, the tabulation shows also that in a larger number of cases it was the sinus operation made originally to relieve a chronic infection, perhaps with polyp formation, which precipitated the development of severe asthma. Sinus surgery still remains as a difficult and very troublesome problem.

In certain instances the "cure" which persisted, perhaps for as long as

ten years, was followed by a recurrence of asthma later and then after a time the state of cure returned again. This fact gives strong support to the idea that asthma depends upon a disturbance of some sort which is fundamental and which is always present. These patients have a "weak spot" which is asthma, and this "weak spot" flares under provocations of all sorts including allergy as one of the precipitating factors.

As this clinical study goes on it begins to look as though asthma is a disease and not merely a symptom. Whether this narrower concept will make us less ready to look for special causes in certain groups of cases, and so, perhaps, will make us miss something, or whether on the other hand it is proper to let our classification apply only to the exciting factors, and so to encourage the belief that asthma in the "young lady" is the same disease as asthma in the "old gentleman," is still doubtful. Surely it is hard to believe that the wheeze which comes to the young school girl for a day or two in the middle of the ragweed season is the same disease as that which develops suddenly in the tired business man or in the harassed housewife and pushes them down to the depths of depletion and despair.

The problem is still wide open: the approach to it is not at all clear.

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BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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MAHLON ASHFORD, *Editor*

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THE ROYAL SOCIETY OF MEDICINE

Patron : HIS MAJESTY THE KING.

1, WIMPOLE STREET,
LONDON, W.1

March 6th 1947.

Dear M^r President Baehr.

It is with very great pleasure that I send, by the hand of Lord Horder, Honorary Fellow of the Royal Society of Medicine, Greetings from our Society to the New York Academy of Medicine on the occasion of the Celebration of the Hundredth Year of its service to the Profession whose needs called it into being in 1847.

It gives the more satisfaction to us in the Royal Society of Medicine to greet the Academy, that in it we recognise and honour a Body whose age and whose ideals of service to Humanity are the same as our own.

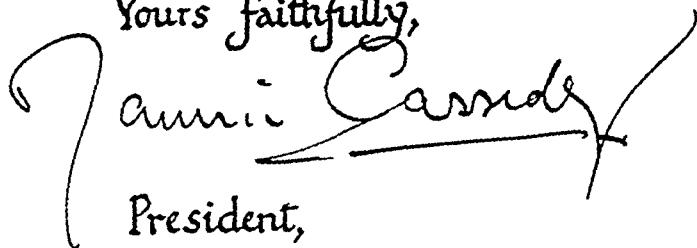
In these times of global stress and

perplexity, when all Nations of the Earth need spiritual, no less than physical, rehabilitation, our Profession is called upon to play a leading part in the restoration of the World to mental and physical health. This task is one in which the New York Academy of Medicine will add gloriously to its great achievements of the past Century.

The Royal Society of Medicine wishes the New York Academy of Medicine Prosperity, Courage and Success in its high endeavour, and it welcomes this opportunity of strengthening the bonds of friendship and co-operation which link our Institutions and the individual Members of them, thanks to our common language, traditions, aims and ideals.

Believe me, my dear Mr President,

Yours faithfully,

A handwritten signature in dark ink, appearing to read "J. Amis Carrsdy". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

President,
Royal Society of Medicine.

This letter from the President of the Royal Society of Medicine of London to the President of The New York Academy of Medicine, was brought to this country by Lord Horder and was read by him on the evening of March 21st, just preceding the address which he delivered at the conclusion of the Institute on Social Medicine as part of the ceremonies commemorating the 100th Anniversary of the Academy.

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



JUNE 1947

SOCIAL PATHOLOGY AND THE
NEW ERA IN MEDICINE*

JOHN A. RYLE

Professor of Social Medicine, Oxford University

"Into those other fields of endeavour as we gaze, we see numberless close analogies to our own work. We see there another Pathology than that which our clinics and dead-houses teach us, yet a Pathology almost parallel in its teachings."†

THE term social pathology, in the sense in which we have come to use it, is not a new one. No one, perhaps, had the idea of social pathology more clearly in his mind than that great medical administrator, historian and man of science, Sir John Simon (1816-1904). The term was also employed by Alfred Grotjahn (1869-1931), the first Professor of Social Hygiene in the University of Berlin, who made it the title of a text-book. It has sometimes been given a restricted interpretation, linking it particularly with the study of delinquency, inebriety, vagrancy and crime, but for this restriction I can see no real justification.

Social medicine and social pathology should, as their names suggest,

* Delivered at the Centenary Dinner of The New York Academy of Medicine at the Waldorf-Astoria Hotel, March 6, 1947.

† Sir John Simon, "English Sanitary Institutions."

be considered respectively as the medicine and pathology of families, groups, societies or larger populations. Just as human pathology is the related science of clinical medicine—whether it be pursued by the morbid anatomist or the physician, in the laboratory or at the bedside—so may social pathology be viewed as the related science of social medicine, whether it be pursued in the office of the statistician or with the aid of socio-medical surveys or experiments, or of other more intimate and specific types of enquiry.

If clinical medicine is a comprehensive term—for it may imply both clinical practice and the theory or discipline necessary for the advancement of knowledge and the improvement of practice—social medicine is even more so. It embraces, on the one hand, the whole of the activities of the public health administration and of the remedial and allied social services, and, on the other, the special disciplines necessary for the advancement of knowledge relating to sickness and health in the community. Of these disciplines the more fundamental may be included under the general titles of social pathology and hygiology.

HISTORICAL COMPARISONS

We can carry our analogy further. Historically, the first developments of human pathology as a separate science were in the field of morbid anatomy. The first morbid anatomists were those great physicians—including, in my own country and my own school, Bright, Addison and Hodgkin—who, in the first half of the last century, realised the need for a closer study of morbid changes and processes and of the causes of death by means of the detailed *post-mortem examination*. Similarly the first scientific development of social pathology was the *social post-mortem examination*, as systematised, also in the first half of the last century, by William Farr and evolved by him as a mathematical refinement of the broad and historic social surveys of Edwin Chadwick. The two great branches of human pathology thus had their beginnings almost simultaneously. The social post-mortem examination employs statistical methods and techniques to reveal death-rates and their trends in the population, whether from all causes or from specific causes, and these rates and trends can be correlated with social factors and social change. It has this advantage over the individual necropsy: that it succeeds in shedding light upon the predisposing or *ultimate* (as distinct from the *intimate* or specific) causes of the prevailing social diseases,

as well as upon their incidence and distribution. The individual necropsy may reveal the extent and character and processes of a disease and the final cause of death, but it is silent about the circumstances which led to the development of the original morbid change.

The later progress of human pathology (as we ordinarily use the term) has required the advancement and co-operation of such sciences as bacteriology, immunology, protozoology, haematology and biochemistry. Radiology, endoscopy, physiological techniques and surgery have further assisted the study of the pathology of the living, and so have many careful clinical observations bearing upon the natural history and symptomatology of disease. Social pathology, too, has required the emergence and adaptation of associate methods—of methods of clinical, social and more specialist enquiry. Its epidemiological studies are concerned with the incidence and trends of diseases in the living community or its component groups, and with correlations of these with season, climate, race and environmental and social conditions. With a wider collection and fuller utilisation of statistical material relating to all the commoner types of disease and injury—and not merely to those due to crowd infection and connected especially with childhood, insanitary conditions and war—the horizons of epidemiology will by degrees be greatly expanded. Already analyses of official and other figures from various sources have considerably increased our understanding of some of our more chronic diseases and their distribution. In a more specific way *socio-medical surveys* are now likely to be applied in increasing measure to the refinement or extension of the findings of mortality and morbidity studies based upon official returns; to comparative studies of the health and sickness experience of different geographical, social or occupational groups within a population; to the investigation of the incidence and aetiology of particular diseases; or to the study of growth, development and sickness rates in infancy and childhood under varying economic and nutritional conditions. The method of survey thus makes use of “natural” experiments, just as the physician avails himself of “natural” experiments in studying the phenomena of disease in individuals. The survey has this advantage over the clinical investigation of the hospital ward, that it deals with larger numbers and can study simultaneously the incidence and manifestations of disease and health and borderline states in a community and relate them more directly by parallel enquiries to various causal influences. Hygiology—the study

of-health and its causes—is clearly an associated interest of those who employ the survey methods of social pathology.

The third stage in the evolution of laboratory pathology witnessed the growth of *the experimental method*, employing animals and sometimes men. It has made far-reaching and valuable contributions to individual and special pathology, with important consequences for medical practice. The use of controlled *social experiments* in human populations also has important possibilities. Experiments of opportunity and planned experiments can both play their part. At times of rehousing, during industrial reorganisation, in schools or other institutions, and in the armed forces, opportunities arise of utilising changes of environment, employment or management and studying their effects on the health and sickness of partially closed communities. Sometimes a comparable population whose conditions remain, for a sufficient period, unaltered provides an additional check. The experiment of M'Gonigle and Kirby (1936) was a notable example of the experiment of opportunity and helped to direct immediate attention to the relative importance of nutritional opportunity and housing in maintaining or jeopardising the health of urban communities. These authors, during a time of economic depression, seized the opportunity of studying over a period of years one half of a slum population which was moved to a new housing estate, the other half remaining as a control. The health and mortality experience of the transferred population showed a significant deterioration. Higher rents and the cost of travel into town reduced the budget to such an extent as to leave too small a sum-for sufficient and balanced diets.

In the services and in schools and in industry it should be possible, from time to time, to design and stage experiments having specific objectives and provided with adequate controls. It will never be possible to reproduce the precise conditions of the epidemiological studies of Greenwood and Topley on mouse populations, but human social experiments may nevertheless come to have considerable value for preventive medicine and social planning. Changes of human or psychological environment should be as important to study as changes in the material environment.

THE STUDY OF GROUPS

The groups or "populations" which are subjected to survey or ex-

periment at the hands of the social pathologist may be determined by age, as in the case of infants or schoolchildren or university students; by sex, as in the case of housewives or expectant mothers; by occupation, as in the case of factory workers; by age, sex and occupation, as in the case of army recruits; by geography, as in the case of a village or island community. A population may be studied in relation to its total health or sickness experience—as, for instance, in the case of an investigation of the growth, health and sickness experience of the pre-school child, from birth to five years of age, which we are conducting at Oxford against the background of varying social opportunity. Another population, say of adolescents, may be studied in connection with its general nutritional status or, more particularly, in order to assess the frequency of a single manifestation of a specific deficiency. As an example of this I would mention a study of thyroid hyperplasia in adolescents (carried out by myself and colleagues for the Medical Research Council) and related with their geographical and geological environments and the iodine content of the drinking waters therein available. A “population” may also be composed of a number of persons suffering from the same disease (for instance, pneumokoniosis or peptic ulcer); in such cases, when aetiological factors or the results of treatment are under consideration, the enrolment of appropriate control populations becomes necessary.

Both branches of pathology, the individual and the social, require their special collaborations. Human pathology involves collaborations between the physician, the laboratory worker and others; social pathology between the physician, the statist, the medical social worker and others.

FURTHER ANALOGIES

I hope I may have succeeded in showing that there are close analogies to be drawn between the histories and the methods of these two sciences. Both have developed and will continue to develop their techniques for the investigation of disease in the living and the dead, and both have recourse to detailed observational and experimental methods. Both may require the assistance of mathematical methods and for social pathology (of which the statist, the epidemiologists and the great social surveyors have been the chief pioneers) biostatistics provide the basic science. The unit of study in the one case is the single human organism;

in the other the human population or social organism—whether this be as small as the family or as large as the nation. The pathological science in each instance is subscribed to by a variety of associate disciplines. In each case old methods must from time to time be modified or adapted, or new methods devised.

Briefly summarised, we may say that individual pathology deals with the quality and effects of diseases and, in practice, assists diagnosis and treatment, while social pathology deals with the quantity and causes of diseases and, in practice, assists prevention. Both sciences have their peculiar value, but as to which is the more likely in the long run to assist the saving of life and health and to encourage the more effective protection and development of peoples there can—from the evidence of history—be no real dispute. Their tasks, like those of individual and social medicine, should, surely, by now be more closely integrated.

THE CASE FOR ACADEMIC STATUS

In one respect the comparisons which have been drawn are incomplete. Human pathology, in its usually accepted sense, has acquired a status of its own in the medical faculties of all universities. Its associate sciences are commonly housed close together or even under one roof. Its numerous workers are given the opportunity to contribute to research and to the day-to-day teaching of undergraduate or graduate students. Outside a few great research institutes (I speak here of my own country), such as the London School of Hygiene and Tropical Medicine—which have served broader national and imperial needs and have had but a slender association with the life and work of the medical schools or with other scientific departments of the university—social pathology has, until lately, been accorded no position of its own. Its students, whether they work in the fields of public health bacteriology, of epidemiology and vital statistics, or in nutritional physiology, industrial psychology or other subjects, have tended to do so in various places and in detachment and without the advantages of a presiding and co-ordinating discipline. Team investigations of selected populations in relation to their total environment have seldom, until recent years, been undertaken, because organisation for the sampling or enrolment of populations for study was lacking. The epidemiology of diseases other than the fevers, venereal disease and tuberculosis, and more recently of cancer and the nutritional diseases, has scarcely been consid-

ered as a function of workers in the public health field. Its outstanding importance to clinical, constructive and preventive medicine notwithstanding, social pathology has not notably influenced clinical teachers and the regular instruction of the medical student.

Individual and social pathology, like clinical and social medicine, have developed along parallel rather than converging lines. And yet they have surely much to give to one another. Lacking the necessary time and associations for expansion, the medicine of the hospital ward and the research unit has been contracting its field and becoming by degrees an exercise in bedside pathology, pharmacology and therapeutic detail. The broader natural history of disease in man and man in disease has been too little considered. The too prevalent dissociation of academic medicine from psychological and sociological enquiry (without which no patient and no disease can be fully understood) engaged the interest of Cabot (1918) some years ago and has been well commented upon by Canby Robinson (1939), Richardson (1945) and others in your country. Dr. René Sand (1938) in Belgium has been a leading pioneer in the combined disciplines.

It is curious that aetiology, in its wider sense, should have so far lost the interest which it had for the older physicians. While specific agents are still assiduously sought for, the contemporary neglect of more comprehensive enquiry—taking into account the influence not only of specific factors and of age and sex and race and heredity, but also of economic circumstance, domestic environment, occupation, nutrition and education—would, I believe, have attracted the adverse comment of such great physicians as Ramazzini, Trousseau, Fagge, Gull, Wilks and Osler, were these great men to return to us to-day.

These modern trends in medicine have not been good for the training of the undergraduate student or for the thought of his teachers. Have we provided anything better for the graduate student? Have we helped him to a just appraisal of his functions and his problems? In general, the newly qualified doctor embarks upon his career steeped in the ideas of individual pathology, moderately well versed in therapeutic techniques, and with a smattering of psychology, but almost ignorant of social pathology; knowing little of the incidence of diseases and their mortalities and secular trends or of the social factors which are in part or whole responsible for their inception or continuance. His interest in the frequency and the reasons for the frequency of the more prevalent dis-

eases and injuries—whether lethal and crippling, or crippling but not lethal, or of less serious type—has scarcely been awakened. The possibility of preventing them has been too little discussed with him, whether at the bedside or elsewhere. In regard to some important groups of diseases he is actually misled by terminology and his text-books. Cholera, plague, malaria, the dysenteries, leprosy, hookworm and beri-beri have been classified for him as “tropical,” or, perhaps (if they have too recently been familiar nearer home) as “sub-tropical” diseases. And yet they have all occurred and some of them have even flourished in Great Britain and European countries and the temperate zones of the Americas at a time when dirt, poverty, squalor and malnutrition, and ignorance or neglect of sanitary laws were conspicuous among the attendant social influences. These great endemic diseases of backward populations still prevail in India, China and Africa. Nearly all of them are pre-eminently “social” diseases and due to alterable social causes. They are, strictly speaking, linked rather with a stage of historical development than with latitude or climate. The adjective “tropical” (if we except diseases due to parasites and vectors which are only found in the tropics) is a misnomer.

Other and more chronic diseases now prevalent in Europe and the West—peptic ulcer, cardio-vascular disease, cancer, the chronic rheumatic diseases, the visceral neuroses, the psychoneuroses and accidental injuries—also have their epidemiologies and social aetiologies, but this has not been made sufficiently apparent to the mind of the student or practitioner. And yet if a graduate, stimulated by an interest in preventive medicine, desires to enter the public health service, his training for a special diploma has directed his thought too exclusively to the study of fevers and the immediate material environment, to sanitary law and engineering and to public health bacteriology and chemistry. The *living human community* has been insufficiently considered as an object worthy of study, and, outside his brief apprenticeship in vital statistics, he has not been greatly encouraged to consider fundamental methods of enquiry as important to preventive and constructive medicine as histology, physiology and biochemistry are to clinical medicine.

In England the opportunities for a research training and career in social or preventive medicine have in the past been very few and to be found chiefly at such large institutes as the Lister Institute or the London School of Hygiene. The former is mainly devoted to scientific

investigation and standardisation at the laboratory level. The latter, while attracting famous men, providing our best graduate diploma courses and fostering first-class laboratory, epidemiological and environmental research has not directly fertilised the medical schools. New experiments and opportunities in other settings are now needed.

"SOCIAL MEDICINE" AND "PUBLIC HEALTH"

I have scarcely as yet had time to familiarise myself with the organisation of research and teaching in the field of preventive medicine in your universities, and it may be that I have overemphasised the distinctions between what we have long called "public health" and what we now call "social medicine." The main differences, however, would seem to be these:

1. Public health, although in its modern practice attaching an ever-increasing importance to the personal services, for a long time and at first for very sufficient reasons, placed the emphasis on the *environment*. Social medicine, deriving its inspiration more from the field of clinical experience and seeking always to assist the discovery of a common purpose for the remedial and preventive services, places the emphasis on *man*, and endeavours to study him in and in relation to his environment. Furthermore, the immediate material environment, in the shape of housing, drainage and water supplies, is to-day extended to include the whole of the economic, nutritional, occupational, educational and psychological opportunity or experience of the individual or of the community.

2. Public health, in the first instance, and again for obvious reasons, has been largely preoccupied with the communicable diseases, their causes, distribution and prevention. Social medicine is concerned with all diseases of prevalence, including peptic ulcer and the chronic rheumatic diseases; cardio-vascular disease, cancer, the psychoneuroses and accidental injuries—all of which have their epidemiologies and their correlations with social and occupational conditions and must ultimately be considered to be in greater or less degree preventable.

3. Where hospital practice (as distinct from preventive theory and practice) is concerned, social medicine properly takes within its ambit the whole of the work of a modern almoner's department; this includes social diagnosis and social therapeutics—the investigation of conditions, the organisation of after-care and the readjustment of the lives of individuals and families disturbed or broken by illness. The almoner or medi-

cal social worker also has an important part to play in teaching and in the follow-up activities of a clinical research unit.

In brief social medicine extends the interest and alters the emphasis of the older public health, just as social pathology extends the interest and alters the emphasis of earlier epidemiological study.

Accepting these changes of emphasis, can a case be made for the provision of a status for social medicine and pathology in our universities and for research departments working in close association with their medical schools? If so, how should their functions be determined or how developed from those pertaining to existing schools of hygiene and preventive medicine? What nucleus staff will they require? And, finally—and to this question the title of my discourse requires a reasoned answer—what may their influence be upon the evolution and progress of the Medicine of our coming age?

NEW TRENDS AND PROSPECTS

In attempting to answer the questions which I have posed, it occurred to me that a brief account of the Oxford experiment and of some other developments in England might serve our purpose better than theoretical discussion or a mere statement of personal views. I can deal but briefly with descriptions here, but elsewhere I shall give a more detailed account of our experience.

What I have referred to as the Oxford experiment has been in progress for barely four years. Nevertheless, it can be claimed that it is beginning to take shape satisfactorily, notwithstanding its difficult beginnings while the war was still in progress. The staff of my small Institute includes physicians, statisticians, a radiologist and a radio-grapher, a medical social worker, attached workers with nutritional and epidemiological interests, secretarial and clerical assistants, and (together with a regional Bureau of Health and Sickness Records which also comes under my direction in the same building) a unit served by expert records officers, transcribers, coders and technical workers in the Powers-Samas machine room.

With the assistance of the medical officers of health for Oxford city and county, a tuberculosis officer, a physician for maternity and child welfare, a school medical officer, a public health bacteriologist, a factory medical officer, a chief sanitary inspector and the almoners of the Radcliffe Infirmary—all working in the Oxford area—I and my

statistical colleague, Dr. W. T. Russell, have undertaken responsibility for the whole of the undergraduate teaching in social medicine and public health. We provide a course of lectures, socio-medical case-conferences and field visits running through the three terms of the academic year. At the case-conferences we present cases as living texts bearing upon the correlations of disease with social circumstance; the cases are shown in turn by the house-physician or a senior student and by the medical social worker, and are then discussed by the professor and the class. Teaching of this kind helps to forge the essential link between the two disciplines of clinical and social medicine. The lectures, primarily intended for medical students in the clinical period, are open to graduates, medical social workers, health visitors and health visitors in training. The course has replaced the former statutory course of detached public health lectures occupying a few weeks of the year only. The inculcation of principles and the inter-relations of social and clinical medicine seem to me more important at this stage than instruction in the details of sanitary technique and law and administration. Specialist training in all subjects should surely be reserved for the graduate period.

We hold no special graduate or diploma course. I regard the best type of graduate opportunity as that provided (as in other university departments) for a small number of men or women holding senior or junior research assistantships, each working on a particular problem but all sharing in the community of interest which the Institute provides. Our research programmes include, or have included, a continuing child health survey between birth and 5 years and covering all social groups; a statistical study of the stillbirth rate in the population in relation to social and nutritional factors; a study of the effects on parturition of residential ante-natal rest; a study of adolescent thyroid hyperplasia in relation to a positive or negative history of endemic goitre and the iodine content of local waters in various parts of rural Britain; a continuing study of occupational morbidity and accidents in neighbouring factories; a study of peptic ulcer in factory populations; studies of endemic fluorosis and of the fluorosis hazard in the neighbourhood of certain industries which emit fluorine-containing smokes; and a long-term study of student health.

Since 1943 three Departments of Social Medicine have come into being, at Oxford, Birmingham and Edinburgh—the first two with endowments provided by the Nuffield Trust. Three additional Chairs and

Departments of Industrial Medicine—and in an industrial country occupational health and sickness furnish a large part of the problems of social medicine—have also been created by the Nuffield Foundation at Manchester, Glasgow and Durham. Chairs of Child Health have been established in London, Liverpool, Newcastle, Birmingham, Leeds, Sheffield and Edinburgh. The beginnings of life, for very obvious reasons, are particularly worthy of detailed socio-medical investigation. Those chairs and departments for which the Nuffield Foundation makes provision are given endowments for an experimental period of ten years. Thereafter, if they make good, it is to be hoped that they will become a permanent responsibility of the universities concerned.

The case for social medicine as a subject worthy of support in a university setting would seem, in fact, already to have been accepted in Great Britain, and the report of the Goodenough Committee (1944) has done much to foster the idea. I would, however, submit that if these departments are to be fully effective and successful in their contribution to teaching and research and eventually to the improvement of practice and services, two things are necessary. First, they must—with critical regard for the quality of their methods and the maintenance of standards—develop their related disciplines, the methods and techniques of social pathology and hygiology. And secondly, in order to secure ready access to the populations in which they are interested and the collaboration of those immediately responsible for the health of these populations, they must establish a close and friendly liaison with the departments of public health, the medical and welfare departments of industry, the education authority and the medical officers of the school services, and others. They should also maintain an association with the hospitals and science departments of the university cities in which they are established. For instance, clinical medicine and departments of both social and physical anthropology may well have overlapping interests with an institute of social medicine. Any tendency to academic isolation would at once render abortive the work of a department devoted to socio-medical enquiry. Teaching in social medicine and pathology should be available for the student throughout the clinical period of his training and should wherever possible be related to his bedside teaching.

The expansion or modification of existing programmes by established schools of hygiene and the essential two-way linkages with the clinical

worker and with the field worker in public health or industrial medicine may not be easy to bring about. Nevertheless, the experience which we have gained during the last four years at Oxford compels me to the belief that there is a case for other experiments—not necessarily identical in type—in the medical faculties of other universities. Only time can show how far our English programmes will justify themselves. Appropriate research staff and men with the training and outlook necessary for the post of director in such departments are not at present plentiful. Where such senior posts are in question, long clinical and teaching experience is probably at present more important than public health or industrial experience, for socio-medical investigations are largely concerned with human assessments and socio-medical instruction should be related constantly to patients and their problems and to the natural course and consequences of disease. It is, however, much to be hoped that public health men will also be attracted into the field and that students from departments of social medicine will enter the public health service.

In the matter of staffing I would say that whatever specialist additions may later be found necessary, the personnel of a department should include physicians, biostatisticians, medical social workers and, probably, a radiologist. The need for a nutritional or occupational physiologist or a social psychologist will be determined by the types of investigation undertaken or by the availability of colleagues working in neighbouring departments. For instance, a study of postural defects in school and pre-school populations—and how can we ever advance our knowledge of their aetiology by studying the end-result material which reaches hospital?—would clearly require the collaboration of an orthopaedist, but it is unlikely that a department of social medicine would have a place on its staff for a whole-time specialist in this category. It might well, on the other hand, employ one or more whole-time paediatric research workers, for we cannot over-emphasize the importance of the study of early life and its special hazards within its varied social settings and of ostensibly healthy children. The study of occupational problems in industry or the home might call for quite different types of enquiry from those at which I have hinted. For instance, in the particular problems relating to man and the machine, or the housewife and her tasks, the physiologist with wartime experience of human adaptation to the tank and the aeroplane might supply valuable experience.

Under our new National Health Service the country will, for the purposes of administration and the hospital service, be divided into a number of regions. Where possible, a university with a medical faculty will provide a parent hospital for the region and help to influence the quality of the service and to provide what might be called its medical intelligence bureau. It would seem to me that a university department of social medicine could come to have high value, both academic and social; could maintain a co-ordinating interest in the vital statistics and survey work of the area, and assist in the study of the particular hazards for the peoples of the region created by main industries or retarded social development. Retaining academic liberty and without coming within the immediate sphere of state administration, it could yet have a healthy influence upon the conduct of an evolving service, could help to encourage salutary emulation as between regions, and—with the aid of its statistical and records departments—serve perhaps, as a local Registrar-General's office in miniature and provide therein a training for biostatisticians and research apprenticeships for physicians and medical social workers.

THE FUTURE

I come lastly to the most important and yet the most difficult question which I have set myself to try and answer. Speculation is not my habit, but this great centenary gathering, this hour in history which we all hope to look back upon as a moment of pause between two eras—a bad one and a better—tempt me to invite my native optimism and emergent ideas to go into partnership for the occasion. "What," I have asked, "may be the larger influence of these new directives for medical and social thought and action? How, possibly, will they assist the general evolution of Medicine in the new age that lies ahead of us?"

Our great contemporary biologist and humanist, Julian Huxley (1944), has discussed the transition now in progress from the age of "economic man" to the age of "social man." Our profession, which is so particularly concerned with man and his welfare, must assist this transition with all the scientific and humanist wisdom at its command. Hitherto, our science, like our practice, has evolved along individualist lines. Whatever the several countries may do with regard to the modification of their systems of practice and of service, it seems to me that the scientific study of health and disease in man—the most complex of

all social animals—must henceforward concern itself to an ever-increasing degree with the interactions and correlations of disease and health with changing social circumstance. Socially, industrially, politically, we are creating a new age. With it, inevitably, we alter the whole character and distribution of diseases and set ourselves new problems for solution in the fields of medical science, practice and administration.

Some of my friends have rebuked me for leaving the clinical fold. I reply in effect that I have merely taken the necessary steps to enlarge my field of vision and to increase my opportunities of aetiological study. My allegiance to human medicine is in no whit broken. I wish I could convey to them and to you some of the sense of stimulation and rejuvenation that my close association with statisticians and medical social workers and with men and women in the public health and industrial health services has brought to me. Thirty years of my life have been spent as a student and teacher of clinical medicine. In these thirty years I have watched disease in the ward being studied more and more thoroughly—if not always more thoughtfully—through the high power of the microscope; man in disease being investigated by more and more elaborate techniques and, on the whole, more and more mechanically. Man, as a person and a member of a family and of much larger social groups, with his health and sickness intimately bound up with the conditions of his life and work—in the home, the mine, the factory, the shop, the office, at sea or on the land—and with his economic opportunity, has been inadequately considered in this period by the clinical teacher and hospital research worker. The medicine of the teaching schools has, as I have suggested, undergone a gradual conversion to a highly technical exercise in bedside pathology and therapeutic method. The morbid “material” of the hospital ward consists very largely—if we exclude the emergencies—of end-result conditions for which, as a rule, only a limited amount of relief repays the long stay, the patient investigation and the anxious expectancy of the sick man or woman. With aetiology—the first essential for prevention—and with prevention itself the majority of physicians and surgeons have curiously little concern. Nor have they at present the opportunity, nor yet the appropriate types of training or assistance, requisite for the study of aetiology or prevention. Their material is mainly selected by four factors: the gravity, the difficulty or the rarity of their cases, or their suitability otherwise for admission to a hospital. Some of the most common diseases, the less lethal diseases and

the beginnings of disease are even considered as providing "poor teaching material." Health and sickness in the population and their possible correlations with significant and measurable social or occupational influences are outside their province.

Reverting, for a moment to the question of the prevalent non-communicable diseases, our modern endemics, let us take as an example a particular type of disease—one in which I have long been interested: gastric and duodenal ulcer. We have watched these diseases—which were at one time, judging by earlier records of the clinic and the dead-house, relatively rare—becoming in the course of two generations two of the most common of all. Their incidence is still rising. If the combined total of living persons who have or have had an ulcer in America and the British Isles could be computed, they would be found to number not tens or hundreds of thousands but millions. Every endeavour, orthodox and unorthodox, medical and surgical, has been made to discover a cure, but with no very outstanding or encouraging results. Animal and laboratory experiments have carried us but a very little way in the assessment of cause. And yet the causes (for ulcer will probably find its place among the "multiple stress" diseases) must have been developing contemporaneously with rising incidence. A disease which was once rare can become so again. Until we study the victims of the disease at first hand and in relation to their work, their total occupational experience, their communities, their food, their habits and anxieties, and their innate predispositions, are we likely to obtain the answer to our question?

And here, briefly, are some other examples from among our outstanding socio-medical problems of to-day. One of my statistical colleagues has lately shown that there is strong evidence of relationship between the stillbirth rate in England and Wales (at present depriving us annually of some 20,000 potential citizens) and the nutritional experience of a population (Sutherland, 1946). Before the war the infant mortality at 3–12 months in the unskilled worker group in England and Wales, a mortality sustained largely by environmental conditions, was four-and-a-half times that in the professional classes. Rheumatic heart disease, like tuberculosis, has a close correlation with poverty and crowding. The mortality from gastric and skin cancers among the working classes is twice as high as that in the professional classes. Angina pectoris—and coronary disease is taking a higher toll each year—has a death-rate

among doctors that is twice as high as it is among bank and insurance officials and nearly twelve times as high as it is among agricultural workers. Facts of this kind should surely be known to every medical student. Until they are known and widely discussed and subjected to further analysis, the appropriate education of the profession and the public and the enlightenment of the legislature cannot follow and necessary protective measures and social planning must inevitably be delayed.

One of the most disturbing thoughts in our present age is the long lag between the arrival of new knowledge and necessary action. In some directions you tend to move faster in America than we do. We still have to confess that milk pasteurisation in England is far from universal. We payed for this delay recently with some 600 childhood deaths from bovine tuberculosis and 2,000 non-fatal cases in one year. Although the diphtheria immunisation crusade is now steadily extending, we have also to admit that the deaths from this preventable disease among children during the war years exceeded all those due to enemy action. In all countries infectious disease and poor nutritional opportunity take too high a toll of the working classes. In England we have shown during the war what a fair distribution of food can do even in otherwise exacting circumstances. With our declining birth-rates and ageing populations in Europe and the West, we cannot afford to neglect the study of how we may further reduce, in particular, our ante-natal, infantile and childhood deaths.

PREVENTION OR CURE?

For a very long time we have accepted the old adage "Prevention is better than cure." In our new era the belief in it—for of its truth there can be no doubt—must be made ever more manifest in our research and its directives and in our teaching. The most conspicuous interest of the student ten or twenty years hence will, I hope, no longer be in the rare or difficult and too often incurable case, but in the common and more understandable and preventable disease. May the daily questions on his lips become not "What is the treatment?", but "What are the causes?" and "If preventable, then why not prevented?"

The study of the ultimate causes of disease—the protocataclytic causes, without which the specific factors can never find their opportunity—goes hand in hand with the study of the causes of health, and how much we have still to learn of the meaning and measurement of health. When

social pathology and hygiology come into their own we may witness a return—but this time with fuller scientific authority for the guidance of the people and their teachers and rulers—of that ancient pride in health as a cultural objective which has been largely in abeyance since the days of the old Greek civilisation.

The training of the doctor, which began with observations on and the care of the sick individual, is due now for a great forward stride. Observations on whole communities, whether great or small, (or on appropriate samples) and improved health provisions for them, must henceforward become the prior objective. The individual is not likely to suffer neglect in the process, for all communities are composed of individuals. For generations yet we shall doubtless continue to build our costly hospitals and clinics, and require our armies of practitioners and ancillaries, but meanwhile we must at least embark upon the crusade which will end in the steady reduction of waiting-lists and the closure of hospital wards, and which will eventually put the physical, mental and moral health of peoples before their material wealth. In that crusade—whether by our researches, by realistic reforms in teaching, by the better education of the people or direct representations to government—it is our first duty as physicians to explore and prepare the way.

I submit that we can only do this effectively by electing to pursue the study of social man in sickness and in health as assiduously as we have hitherto pursued the study of individual man in the isolation of the consulting room or the hospital bed, when health has finally passed him by. The quality of our actions and our practice and of our leadership in social reformation will depend, as in the past, on many disciplines, but not least, perhaps, upon the science whose history I have briefly sketched and whose province I have endeavoured to define.

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CARCINOMA OF THE LUNG: A SIX YEAR STUDY*

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THE outlook for a patient who develops carcinoma of the lung is so miserable that many doctors consider it completely hopeless. Because until recently primary carcinoma has been thought to be a rare disease, the possibility of its presence is too often overlooked by the general practitioner. Only after a protracted period of waiting for a turn for the better which fails to occur is he forced to realize that he is dealing with something more than an inflammatory process. Too often, even when the possibility is considered, there is a tendency to procrastinate, in the conviction that, if a tumor is present, the patient is in any case doomed. This tendency is increased by the fact that these lesions frequently occur in heavy smokers whose early symptoms are masked by a long history of cough, and whose illness apparently begins with symptoms of acute infection, symptoms which respond deceptively well to sulfonamide or penicillin treatment. The discomfort of bronchoscopy is a small thing to ask of a patient who is faced with possibility of death from this disease, yet it is surprising how often the chance it affords of establishing the diagnosis early is withheld.

There is now no doubt that the incidence of bronchiogenic carcinoma is increasing. It must be considered as a real possibility whenever persistent cough, chest pain or blood tinged sputum is present, or whenever an unexplained area of density is seen by x-ray which does not clear promptly and completely. Early recognition, as in all malignant tumors, is the key to successful treatment, and it is now certain that surgical treatment can be successful, though the proportion of those cured is still tragically small. In order to gain a clear picture of the situation to guide us in knowing what to expect and to determine how to save more of these patients it is necessary to review the entire picture, rather than to present results in selected groups.

* Read 6 December 1946 before the Section of Surgery of The New York Academy of Medicine.

Vital Statistics: This record presents a review of the experience in an urban teaching hospital of twelve hundred beds, over a period of six years. The records of all patients discharged from the Presbyterian Hospital in New York with a diagnosis of bronchiogenic carcinoma between January 1, 1940 and December 31, 1945, have been reviewed. There were in all 125 patients in whom the diagnosis was made, constituting about 6 per cent of the discharges from the medical and surgical services; in 103 the diagnosis was proved by microscopic examination and in the remaining 22 it was made on evidence from the findings on x-ray, bronchoscopy and clinical course. The high proportion of male to female patients reported in other series was also present in this group, there being 109 men and 16 women, a proportion of nearly 7 to 1. The youngest patient was 34 and the oldest 79, with the usual peak in the 6th and 7th decades. Those operated upon averaged 53 years. Undifferentiated tumors, classified as carcinoma, were slightly more frequent than the better differentiated epitheliomas, but the latter were almost twice as frequent in the operable group, and all of the surviving patients had this type of tumor. The anaplastic "oat cell" tumors constituted only 11 per cent of the entire group, and only one was resectable.

Symptomatology: The symptoms most frequently encountered were cough, pain and hemoptysis, and varied widely with the site of the tumor. In several, metastases caused the first symptoms, six cases first manifesting themselves with cerebral symptoms. Ten patients had no localizing symptoms, complaining only of weakness and loss of weight; several of these were moribund on admission and the accuracy of the history is doubtful. In general the duration of symptoms before admissions was less in the group not operated upon (an average of 5 months in the 79 cases giving a reasonably accurate history) than in the operated group (6.9 months) and it was longer in the resectable cases than those which could not be resected (7.3 months against 5.5 months). This suggests that the resectable tumors are a slower growing group, and corresponds to the higher percentage of well differentiated epitheliomas among them.

Operability: Two-thirds of the group (83 patients) were not operated upon, either because they were not referred to a surgeon, because they refused operation, or because they presented evidence of metastases on admission. No patient was refused operation because of age or because of evidence of chest wall invasion or the presence of pleural fluid

TABLE I

NO OPERATION 83 Patients 66.4%				OPERATION 42 Patients 33.6%			
DIAGNOSIS PRESUMPTIVE 22 Patients 17.6%		DIAGNOSIS PROVED 61 Patients 48.8%		NO RESECTION 13 Patients 10.4%		RESECTION 29 Patients 23.2%	
BRONCHOS- COPY 15 Patients 12%		X-ray 7 Pat. 5.6%		DIED OF DISEASE 12 Patients 9.6%		DIED OF OPERATION 10 Pat. 8%	
AUTOPSY 12 Patients 9.6%		BIOPSY 49 Patients 39.2%		DIED OF DISEASE 12 Patients 9.6%		DIED OF METASTASIS 17 Patients 13.5%	
METASTASIS 12 Patients 9.6%		PLEURA 10 Pat. 8%		PRIMARY TUMOR 27 Patients 21.6%		A -3 2.5 %	
TOTAL 125 PATIENTS							

unless the latter contained masses of tumor cells. Bronchoscopic evidence of tracheal distortion or mediastinal widening was not considered a contraindication, a point of view justified by the fact that one of the patients who remains well showed marked distortion of the trachea. In several instances, however, these considerations were a factor in deciding against operation without surgical consultation. Definite tissue diagnosis was not considered essential, in fact its lack indicates a peripheral and therefore more favorable growth, as demonstrated by the fact that no positive biopsy was obtained in 22 of the 29 resected cases.

One-third of the entire group (42 patients) were operated upon, and resections were completed in over two-thirds of them (29 patients). The remaining 13 patients were found to have extension of the primary growth into the hilar mediastinum, the spine, or widespread mediastinal lymph node involvement. Local extension into the chest wall or pericardium was not considered a contraindication to resection, block resection being carried out in 8 cases.

Pneumonectomy was carried out in 17 cases. In four the lesion was considered either of doubtful malignancy or sufficiently well localized to be removed by lobectomy. Since all of these tumors recurred, it is doubtful if such a limited resection is justifiable and it has been abandoned. In 7 cases portions of the chest wall were resected with a lobe and in one of these a large portion of pericardium also; in one case pneumonectomy was combined with chest wall resection.

Results: The end result in 39 cases was not recorded, but since these patients all had advanced lesions and were failing rapidly when last seen it is assumed that they died. Twenty-six of these received only diagnostic and symptomatic treatment, thirteen received radiotherapy. Of the 44 followed up to death five received no specific therapy. The average duration of life in this group was less than two months, but this figure is influenced by the fact that half of the group (13 patients) were admitted as terminal cases. Two patients in this group survived more than a year, both having squamous cell epithelioma. It may be questioned whether these patients, both of whom were denied operation because of bronchoscopic evidence of tracheal distortion, might have been candidates for resection.

Thirty patients received radiation therapy only, and three others received radiation after thoracotomy had demonstrated that the tumor could not be removed. One of the latter patients was still alive but failing

TABLE II

	<i>Presumptive</i>	<i>Proved No Op.</i>	<i>Inoperable</i>	<i>Resected</i>	<i>Total</i>	<i>Per cent</i>
SEX						
Male	17	51	13	28	109	87
Female	5	10	0	1	16	13
<i>Total</i>	22	61	13	29	125	
	17.6%	48.8%	10.4%	23.4%		

TABLE III

<i>Age</i>	<i>Presumptive</i>	<i>No Op</i>	<i>Exp. Only</i>	<i>Resected</i>	<i>Total</i>	<i>Per Cent</i>
30-39	0	3	0	0	3	2.4
40-49	3	7	6	6	22	17.6
50-59	9	22	3	15	49	39.2
60-69	8	23	4	8	43	34.4
70-79	2	6			8	6.4
<i>Total</i>	22	61	13	29	125	

TABLE IV

CELL TYPE	<i>No Operation</i>	<i>Exploration Only</i>	<i>Resected</i>	<i>Total</i>	<i>Per cent</i>
Oat Cell	8	3	1	12	11
Carcinoma*	33	7	10	50	49
Squamous Epithelioma	20	3	18	41	40
<i>Total</i>	61	13	29	103	
<i>Per Cent</i>	59	12.6	28.3		

* Includes Adenocarcinoma and undifferentiated Epithelioma

rapidly, with widespread metastases when last seen fourteen months after operation, having had a full course of therapy to his primary lesion and another to spinal metastases with great symptomatic relief. The average duration of life after radiotherapy was 6.5 months which is not significantly greater than the average life of the patients (excluding terminal admissions) who received no specific therapy. It should be brought out, however, that many of those so treated did not receive adequate dosage, since the therapy was not continued if palliation of symptoms did not occur early in the course. Definite palliation was accomplished in a number of cases, and it seems probable that in these the duration of life was prolonged. No patient gained prolonged palliation or apparent cure.

Of the 42 cases operated upon 13 were not resected. One died post-operatively and the remainder died an average of 5.5 months after operation. This corresponds with the average life expectancy of the unoperated group (excluding the terminal cases) so it may be concluded that, except for the operative mortality, exploration alone does not shorten life expectancy. Nine of the 29 resected cases died in the post-operative period, a mortality of 31 per cent. This mortality may be expected to improve with time, especially since the all important immediate postoperative care of the patients in this group was hampered by the fact that it had to be carried out with a staff depleted by war. Of the twenty survivors, fourteen died of metastatic disease. One patient died of pulmonary insufficiency but was found at autopsy to have a small metastatic liver nodule. Another, who had had an oat cell tumor removed by pneumonectomy, died nearly two years later of carcinoma of the larynx. It is possible that this represented an independent neoplasm, but since both tumors were anaplastic he is grouped with those who died of metastases. One patient who was still alive when last seen, but failing rapidly, with evidence of mediastinal metastases, is also grouped with those who died of metastases. The average life span of these seventeen patients after operation is 15.8 months, a very significant increase over the approximate six months otherwise to be expected. Furthermore the symptomatic relief gained during this period is much greater than the best palliation obtained by radiation. These patients were definitely benefited by their operation even though not successfully relieved of their disease.

Three of the twenty patients who survived resection are alive and

TABLE V

Operation	Average Age	Duration of Symptoms	Duration of Survival	Post-Op Deaths		Died of Disease		Apparent Cure		Total	
				No.	%	No.	%	No.	%	No.	%
Pneumonectomy...	56	6.6	10.8	7	41	7	41	3	18	17	40
Pneumonectomy Resection of Chest Wall	45	5.5	0	1	100	0	0	0	0	1	2
Lobectomy Resection of Chest Wall	57	9.5	10.6	1	14	6	86	0	0	7	17
Lobectomy ..	52	7	32	0	0	4	100	0	0	4	10
Exploratory Thoracotomy	52	5.8	5.5	1	8	12	92	0	0	13	31
Total	53	6.9	7.7	10	23	29	69	3	8	42	

apparently free of disease. All had squamous cell epitheliomas removed by pneumonectomy and all three are back working at their former occupations three or more years after operation. The first was a German-American sheet metal worker of 62 who had first noted a wheezing on respiration 9 months before admission. A tumor mass was seen on bronchoscopy protruding from the right middle lobe bronchus which on biopsy proved to be a squamous cell epithelioma. Following pneumonectomy he developed a small cerebral embolus and then an empyema which required open drainage and subsequent thoracoplasty. His wound has now been healed for three years and he carried out a full day's work in a shipyard during the last two years of the war. The second survivor was a Jewish furrier of 40 who had been treated for suspected tuberculosis for 10 months because of repeated hemoptysis. During this period his left main bronchus had gradually become completely obstructed with complete atelectasis of the lung and considerable mediastinal distortion. Following pneumonectomy he developed a small empyema which healed after open drainage. He returned to work six months after operation which is now nearly three years ago. The third survivor is also a furrier, a Greek of 45 who had suffered from symptoms of recurrent pneumonia, yielding to sulfonamide treatment but recurring

as soon as treatment was stopped, for four months before operation. Bronchoscopic examination showed no tumor, but the history and x-ray picture were considered sufficiently suggestive to warrant pneumonectomy, which revealed a squamous cell epithelioma of the left upper lobe. He made a smooth recovery and has been back at work since two months after operation, now four years ago.

SUMMARY

1. A series of 125 unselected cases of primary bronchiogenic carcinoma admitted to a general hospital service over a six year period has been presented.

2. In two-thirds of the group diagnosis was made either at autopsy or so late in the course of the disease that no operation was considered justifiable.

3. Of the group of 42 patients operated upon, it was possible to carry out some form of resection in 29, with a hospital mortality of 31 per cent.

4. Only 3 of the 20 patients surviving resection remain alive without evidence of metastasis, but the lives of those who died of metastasis were prolonged and their symptoms were alleviated.

5. Radiation therapy has not increased the life expectancy in the group treated as compared to those untreated, but in many cases it has relieved symptoms and in some it has probably prolonged life.

6. Three patients are living and apparently well without physical or economic disability 3 to 4 years after pneumonectomy.

RICKETTSIALPOX*†

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DEFINITION

RICKETTSIALPOX is the name which has been proposed for a newly discovered disease of rickettsial origin. This disease is characterized clinically by the appearance of an initial lesion somewhere on the body, usually without symptoms, followed about a week later by the onset of an acute illness of which the chief features are fever, general malaise, backache and headache. Some time between the acute onset of illness and three or four days later there appears a papulo-vesicular rash which may be present on any part of the body. The course of illness from onset of fever until recovery is about a week to ten days and from the appearance of the initial lesion until its disappearance about three or four weeks.

INVESTIGATION

Towards the end of June, 1946, the Department of Health became aware of the occurrence of cases of an undiagnosed illness in a certain section of Queens. Reports of three cases were received from Leon N. Sussman of Manhattan.¹ A number of cases were reported by Benjamin Shankman² and Harry N. Zeller of Kew Gardens. Joan Daly of Forest Hills gave us the reports of some cases that she had seen and Victor Stern of the Riverdale section of the Bronx was kind enough to send us his clinical records of ten cases that he had seen in one large apartment house in the past few years and which he had diagnosed as atypical chicken pox. Reports of isolated cases were received from many other physicians, to all of whom we are greatly indebted.

* From the Bureau of Preventable Diseases, New York City Department of Health.

† Presented at the Pediatric Section of The New York Academy of Medicine, December 12, 1946.

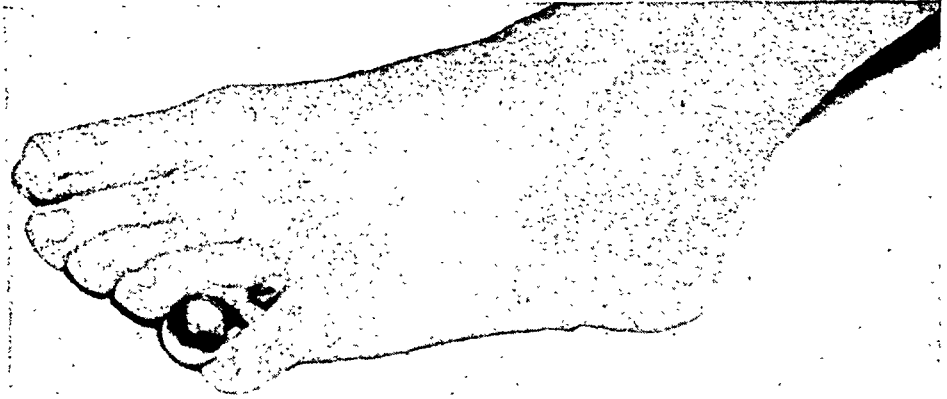


Fig. 1—Initial lesion of Rickettsialpox in interdigital space between fourth and fifth toes. (A button has been placed between the toes to bring out the lesion more clearly.)

In the beginning of July, a preliminary investigation was made in the Kew Gardens section of Queens where most of the cases were located. It soon became obvious that a complete study would require the joint efforts of clinical, epidemiological, and laboratory teams. Charles Armstrong of the National Institute of Health was requested to help in the laboratory work and Robert J. Huebner was assigned to this study. Later, William L. Jellison from the Rocky Mountain Laboratory of the National Institute of Health in Montana joined the team as Parasitologist and remained resident in New York City for a number of weeks in charge of a field laboratory which was set up. This coöperative study worked out very smoothly.

CLINICAL FEATURES

A clinical description of the cases has been reported.³ The important features are three, an initial lesion followed by an acute onset of fever and later by the development of a rash.

1. *Initial lesion:* This is present in most of the cases. However, since the lesion gives no symptoms and since a rash develops later, patients occasionally overlook the initial lesion and confuse it with the secondary rash. Of the patients questioned 72 per cent had noticed the lesion. However, in the cases seen and examined by us 95 per cent showed evidences of a lesion. The initial lesion usually starts as a small papule which is deep-seated and which gradually enlarges sometimes with slight erythematous reaction at the periphery. The papule may be round or



Fig. 2—Initial lesion of Rickettsialpox, lower part of right chest. The lesion is in its terminal stage, only the black eschar being present.

oval and the diameter at its base varies at the height of its development from about $\frac{1}{2}$ cm. to $1\frac{1}{2}$ cm. (Fig. 1). A deep-seated vesicle is always present. It is usually firm, not easily broken and the fluid in it is at first clear but may later become cloudy. The vesicle may be accidentally broken by scratching and some of the fluid exude. At other times, if the vesicle is not broken it tends to shrink and dry. A black eschar forms at the center of the lesion (Fig. 2). This persists for a period of one or two weeks when it drops off leaving a small scar. The entire evolution from beginning to end is about three to four weeks.

The lesion is not tender nor does it itch. There is usually an enlargement of the regional lymph glands and sometimes these are slightly tender to the touch. Lymphangitis, however, does not appear. The initial lesion may occur on any part of the body, but has been seen more often on the covered parts.

2. *Onset of the disease.* This is sudden and is characterized by chills, fever, sweats and backache. It usually occurs about a week after the

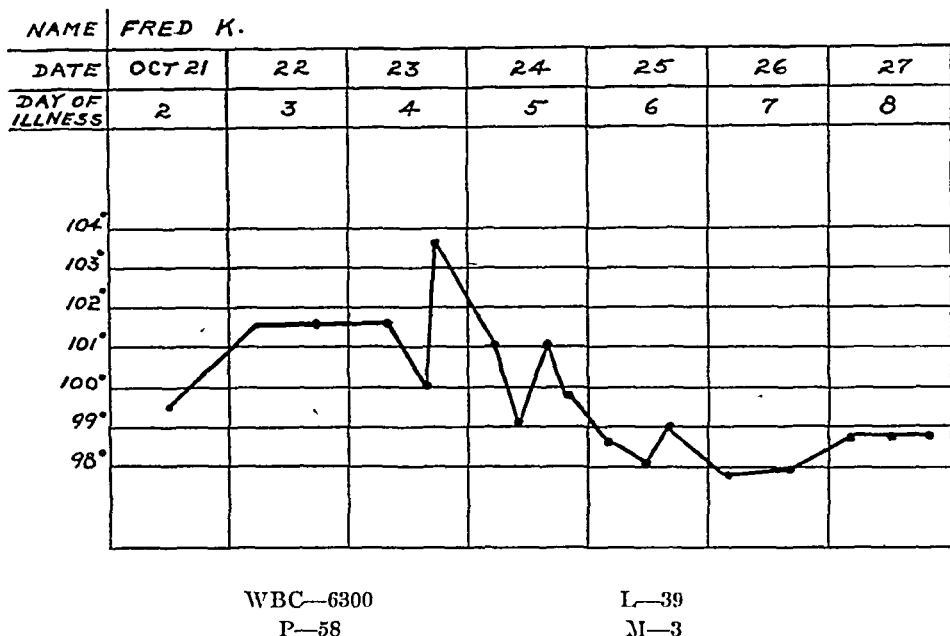


Chart 1—Temperature chart of a case of Rickettsialpox.

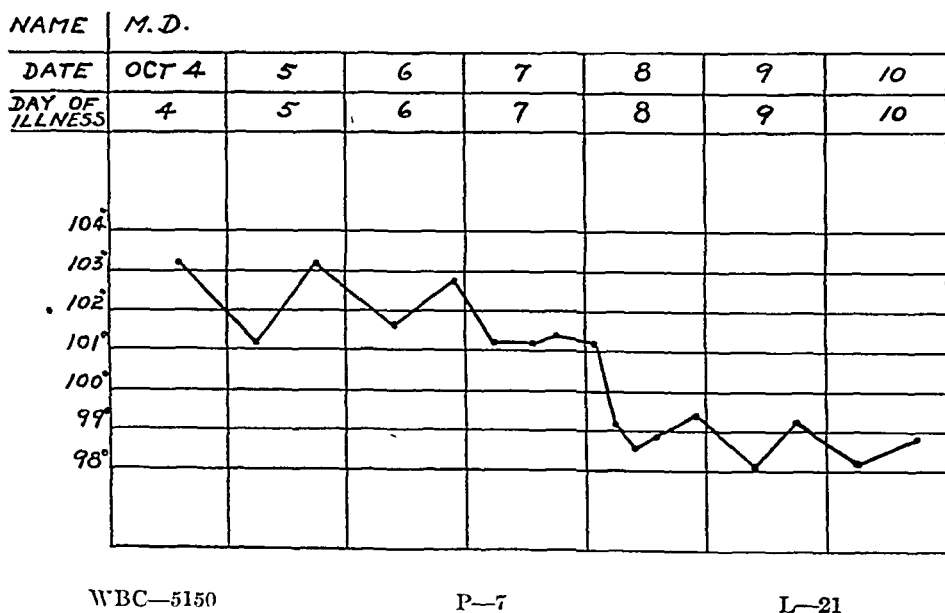


Chart 2—Temperature chart of a case of Rickettsialpox.



Fig. 3—Rash in a case of Rickettsialpox.

onset of the initial lesion. Fever and lassitude occurred in all the cases, headache in about 90 per cent, chills or chilly sensations, usually recurrent, in about 70 per cent, sweats in 75 per cent, backache in 50 per cent and photophobia in 40 per cent. Other symptoms complained of occasionally were anorexia, nausea, dry throat, vomiting and vertigo.

Fever usually rises rapidly to reach 103° to 104° F. about the second day of illness. It persists with remissions for a period of about a week and gradually defervesces (Charts 1, 2). *Chills* or chilly sensations occur, as a rule, in the first two or three days of the disease, occasionally preceding the fever. They usually occur, though not always, in the afternoon; occasionally patients feel well enough in the morning to want to go to work but are compelled to return home in the afternoon. Some of the patients had two chills a day. *Sweats* usually follow the chills. They may be sufficiently drenching to require a change in bed-clothes. *Headache* is frequently complained of and is often quite severe. It is usually frontal; some patients complain of pain behind the eyeballs. Occasionally the complaint is of pain and stiffness in the nape of the neck. In none of the cases, however, was there any question of nuchal rigidity. *Backache* and general soreness of the muscles occur early and

with it there is always present a certain lassitude and a feeling of wanting to stay in bed. Some of the patients complain of *photophobia*. The bright light bothers them. Occasionally a mild injection of the conjunctivae is present. Infrequently there are other complaints, such as nausea and vertigo. Strangely enough anorexia is not a common symptom; patients usually eat fairly well. Nor are there other gastro-intestinal symptoms.

3. *Rash*: The third part of the clinical triad is the rash (Fig. 3). This appears in all cases and is noticed most commonly by the patients between the day of onset of fever and four days later. In those cases that we personally followed, the rash appeared to come on some time after onset of fever. However, many of the patients do not take to bed and do not take their temperature until they have been sick a day or two and they report the rash as occurring on the day of onset. In 90 per cent of the cases investigated, the rash occurred between the day of onset of fever and four days later. The lesions are discrete, erythematous, maculo-papular in character. Usually the papules are either rounded or flat but occasionally appear to be conical in shape. They are always firm to the touch. Surrounding the roughly circular base there is occasionally slight erythema of the skin. A vesicle develops at the summit of the papule in most of the cases. This is firm and dries after a few days, forming a black crust which falls off after another few days without leaving any scar formation. The rash is usually sparse. There is always normal skin between the individual lesions. However, occasionally it is more widely distributed and sometimes almost generalized over the body. No particular sequence of occurrence is noted. In some cases the rash appears first on the face or chest, in others on the back or abdomen, and in still others on the arms or legs. It was seen on the mucous membranes in only two cases, once on the palate and once on the tip of the tongue. It was not seen on the palms of the hands or the soles of the feet. The lesions vary in diameter from about 2 mm. to 8 mm. As with the initial lesion there are no subjective symptoms accompanying the rash. The duration is approximately a week, although in mild cases it lasts not more than two or three days while in severe cases it lasts as long as ten days. As a rule a brownish discoloration remains for a few days after the rash disappears.

In spite of the severity of the acute symptoms and the height of the fever and the discomfort of the chills and sweats, the patients do not

appear seriously ill. There is no evidences of dehydration, no stubborn refusal of food or drink; the pulse is usually good and respirations are normal. In a few cases the spleen becomes enlarged for a short period.

LABORATORY FINDINGS

Normal red counts and hemoglobin determinations were found in the cases. White blood counts showed a moderate leukopenia in practically all cases where they were done, varying between 2400 and 7500 white blood cells per c. mm. The differential smear was either normal or showed a relative lymphocytosis. The leukopenia lasted during the acute illness and the blood returned to normal usually within a week or two after recovery. Urine examinations were normal except for a transient febrile albuminuria in a few cases. Blood cultures were done early in the disease in many of the patients and were repeated in some. All were negative. Sedimentation rates were normal or showed slight elevation. Agglutination tests were performed with blood sera from patients in the acute and in the convalescent stages. They were tested for the typhoid, paratyphoid groups, brucella, *Leptospira icterohemorrhagiae*, *Leptospira canicola*, tularemia and heterophile antibody. These were all negative. In a few cases complement fixation tests were performed for psittacosis. These were also negative.

Agglutination tests were done with the sera of a considerable number of recovered patients for *B. proteus* OX 19, OX 2, and OX K. With exception of a few that agglutinated in low titres, all were negative (Table 1).

Complement fixation tests were performed for epidemic typhus, murine typhus, tsutsugamushi fever, Colorado tick fever and Q fever. These were all negative.*

PATHOLOGY

Biopsies were made of a primary lesion, of skin lesions, and of a lymph node. The pathological picture is reported as similar to that found in lesions of other rickettsial diseases.

ETIOLOGY

Blood specimens were obtained from many of the patients during the acute stage of their disease and inoculated into a variety of labora-

* We are indebted to Dr. Herald L. Cox of the Lederle Laboratories for performing some of these tests for us.

TABLE I—RESULTS OF AGGLUTINATION TESTS OF SERA FROM PATIENTS OF RICKETTSIALPOX WITH B. PROTEUS ANTIGENS

Patient	Date of Onset	Date of Specimen	OX 19	OX 2	OX K
Mrs. C.	3/15/46	7/21/46	neg.	neg.	neg.
Mr. C.	3/29/46	7/24/46	neg.	neg.	neg.
D. M.	5/30/46	9/17/46	neg.	neg.	1:20
M. G.	5/31/46	9/ 7/46	1:20	1:10	1:10
B. B.	6/ 9/46	7/11/46	neg.	neg.	neg.
Mr. S.	7/ 7/46	8/ 8/46	neg.	neg.	neg.
C. F.	7/11/46	9/13/46	neg.	1:20	1:20
M. B.	7/15/46	7/26/46	1:10	neg.	neg.
M. S.	7/17/46	7/21/46	neg.	neg.	neg.
		8/18/46	1:10	1:10	neg.
C. B.	7/17/46	8/29/46	neg.	neg.	neg.
J. M.	7/18/46	8/18/46	1:40	neg.	neg.
L. A.	7/18/46	7/24/46	neg.	neg.	neg.
		8/18/46	neg.	neg.	neg.
M. K.	7/22/46	8/29/46	neg.	neg.	neg.
L. A.	7/22/46	8/18/46	neg.	neg.	neg.
Mrs. S.	7/25/46	8/18/46	neg.	neg.	neg.
H. B.	7/27/46	8/18/46	neg.	neg.	neg.
M. M.	8/10/46	8/30/46	neg.	neg.	neg.
M. A.	8/18/46	8/26/46	neg.	neg.	neg.
		9/11/46	1:40	1:10	neg.
I. M.	8/20/46	8/30/46	1:20	1:10	neg.
M. S.	9/ 6/46	9/13/46	1:10	1:10	neg.
		10/ 9/46	1:10	1:40	1:10

tory animals. An organism possessing the characteristics of a rickettsia was recovered from the tissues of a mouse, inoculated with blood drawn from one of the patients (M.K. strain). The isolation of this organism has already been described.⁴ The name *Rickettsia akari* has been proposed for it.⁵

A second strain of Rickettsialpox was isolated from the blood of another patients (M.S. strain). The latter is culturally and immunologically similar to the M.K. strain. The M.K. organism grows abundantly in the yolk sac of embryonated eggs (Fig. 4). Antigens prepared from this organism were tested by complement fixation with the sera of recovered cases of Rickettsialpox as well as the sera of normal human beings, of recovered cases of syphilis, and of some of the rickettsial diseases, such as endemic typhus, tsutsugamushi fever, Q fever and Rocky Mountain spotted fever. Excepting for cross reactions with Rocky

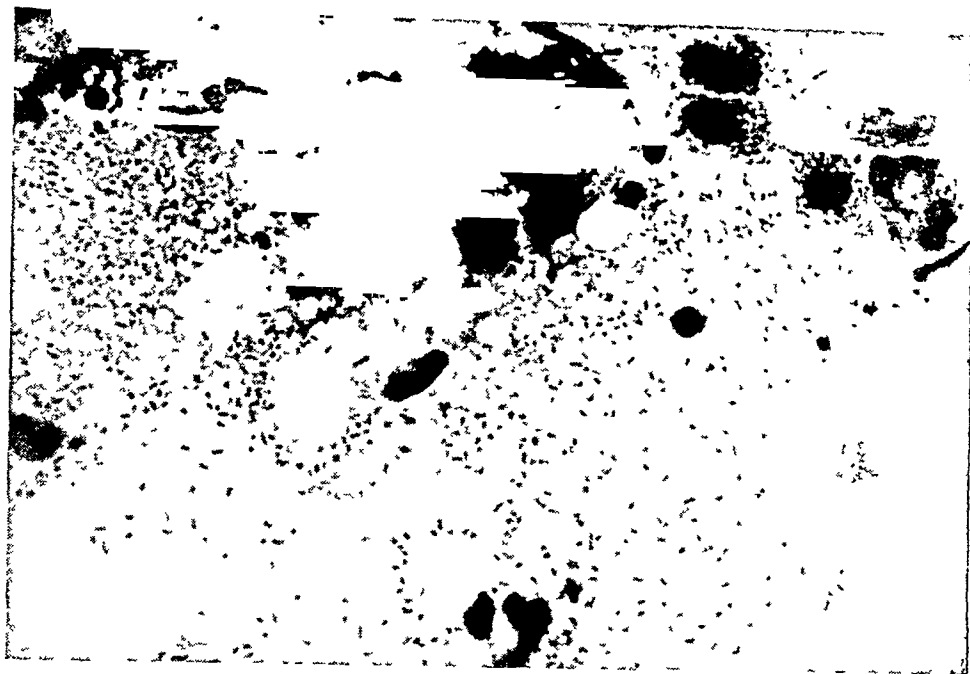


Fig 4—Smear of *Rickettsia akari* from yolk sac. Stained by Machiavello's method.

Mountain spotted fever, a high degree of specificity for recovered cases of Rickettsialpox was shown.⁴ Table II lists some recovered cases of Rickettsialpox. It will be noted that the sera of all were positive by complement fixation for the M. K. antigen. It will also be noted that there is usually cross agglutination with Rocky Mountain spotted fever but as a rule in lower dilutions.

DIFFERENTIAL DIAGNOSIS

1. *Other Rickettsial Diseases.* (a.) *Rocky Mountain spotted fever:* In this disease there is a history of a tick bite in many of the cases. The disease itself is much more severe and mortality is frequently high. The rash is more generalized, often petechial, leukopenia is not characteristic and there is no initial lesion. Furthermore, most cases of Rocky Mountain spotted fever give a positive agglutination reaction for *Proteus* OX 19 or OX 2.

(b.) *Epidemic typhus.* The rash in this disease is similar to that of Rocky Mountain spotted fever. No initial lesion is seen. The patients are usually much sicker than in Rickettsialpox and mortality is usually high. Agglutination of the patient's serum with *B. proteus* OX 19 is

TABLE II—COMPLEMENT FIXATION TESTS OF SERA OF PATIENTS TESTED WITH THE M. K. STRAIN OF RICKETTSIALPOX AND WITH ROCKY MOUNTAIN SPOTTED FEVER ANTIGEN

Name	Date of Onset	Date of Specimen	Titers with	
			Rickettsial Antigen (M. K. Strain)	Rocky Mountain Spotted Fever Antigen
F. M.	5/30/46	9/17/46	1:64	1:16
G. G.	6/25/46	9/19/46	1:32	1:16
W. V.	7/ 5/46	9/11/46	1:64	1:8
R. B.	7/ 8/46	9/30/46	1:16	neg.
J. B.	7/14/46	9/21/46	1:64	neg.
J. D.	7/14/46	9/22/46	1:128	1:64
C. B.	7/19/46	8/29/46	1:64	1:8
C. C.	7/20/46	9/23/46	1:32	1:8
A. G.	7/23/46	9/19/46	1:128	neg.
N. S.	7/30/46	9/24/46	1:128	1:64
F. G.	8/ 1/46	9/22/46	1:32	1:16
E. G.	8/ 2/46	9/19/46	1:16	neg.
J. K.	8/ 8/46	9/22/46	1:64	1:8
L. H.	8/10/46	9/24/46	1:32	1:8
D. G.	8/16/46	10/23/46	1:32	1:8
N. Sh.	8/17/46	9/23/46	1:64	neg.
I. M.	8/20/46	8/30/46	1:32	1:8
		9/11/46	1:32	1:8
E. K.	9/3/46	9/ 7/46	neg.	neg.
		9/11/46	1:4	neg.
M. S.	9/ 6/46	9/13/46	neg.	neg.
		10/ 9/46	1:512	1:512
A. R.	9/22/46	10/ 8/46	1:512	1:256
W. R.	10/21/46	10/30/46	1:4	neg.
		11/ 5/46	1:512	1:256

almost always positive. Furthermore, there is usually a history of lice infestation.

(c.) *Endemic typhus*: While this disease is comparatively mild the rash is macular or slightly papular but not vesicular and usually is generalized following a centrifugal distribution. No primary lesion is seen. Agglutination of the patient's serum with Proteus OX 19 is the rule.

(d.) *Tsutsugamushi fever or scrub typhus*: Although an initial lesion is present in many cases of Tsutsugamushi fever, the rash resembles that of typhus fever rather than Rickettsialpox and it is not vesicular. The course of the disease is more severe and respiratory symptoms occur.

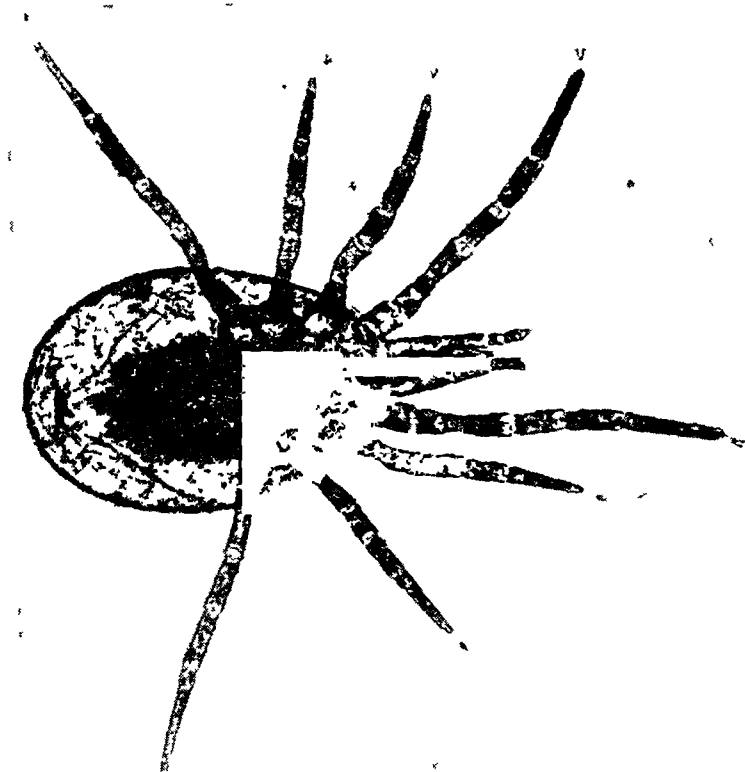


Fig. 5—*Allodeimanyssus sanguineus* (Hirst) adult stage

Infectious Diseases, National Institute of Health, was put in charge.

Mites were recovered from the storage rooms and basements of most of the buildings (Fig. 5). They were found chiefly on the walls, particularly near incinerators. They were also found as ectoparasites of freshly trapped mice (*Mus musculus*) in the buildings. Some of the mites were flat but many were engorged, indicating that they had recently fed. Smears made from these showed mammalian erythrocytes. From two pools of these rodent mites rickettsiae were isolated. The strains were apparently identical with the rickettsia which had been isolated from the blood of two of the patients.⁵

COMMENT

Although the original cases were all reported from one particular housing development in Queens, many other individual and groups of cases have been reported in other boroughs. The investigation of these cases is proceeding. In at least one house in the Bronx where a number of cases of Rickettsialpox had occurred, similar mites (*A. sanguineus*)

were also found on the walls of the basement, and mice were abundant.

The etiology has been definitely established by the isolation of rickettsiae from the blood of patients and from the ectoparasites of mice. The fact that these mites are found in buildings where mice are always present suggests that the mice act as definitive hosts of the mites and that humans are probably infected when they come in contact with and are bitten by infected mites. Control measures will probably depend on methods of elimination of mice and mice harborages from apartments in which they are present.

SUMMARY

The picture of a new disease caused by a hitherto undescribed rickettsia has been given. The main clinical characteristic is the occurrence of a triad consisting of an initial lesion, followed a week later by the acute onset of fever, headache, chills, sweats and backache, and thereafter by the occurrence of a papulo-vesicular rash two to three days after the onset of fever. The duration of illness from onset of initial lesion is about three to four weeks. During the acute illness there is a moderate leukopenia and the sedimentation rate is either normal or slightly elevated. The sera of recovered cases give negative agglutination reactions with *B. proteus* OX 19, OX 2 and OX K, and give positive complement fixation tests for Rickettsialpox, using the M.K. strain as antigen. The causative agent of the disease is *Rickettsia akari* and the vector is a rodent mite, *Allodermanyssus sanguineus*.

There have been no fatalities from the disease.

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PLATO AND CLEMENTINE*

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I HAVE been thinking much, of late, about the word 'normal'—the physiologically normal, the anatomically normal—a word which we use a dozen times a day. Webster defines the normal as that which conforms with natural law, but by this definition only the supernatural is abnormal. This distinction is not very useful to a physiologist, so I have been trying to discover what *I* mean by normal. I am afraid that for all my thinking I have come out by the same door where in I went, but while I was wandering through this labyrinth of thought I have come upon some collateral matters that have perhaps left the experience something better than an absolute loss. I invite you to join me in retracing my labyrinth for whatever the adventure may be worth.

Our use of the word 'normal' in biology and its derivative sciences stems, I think, from the Greek philosopher, Plato, whose name I would put high in the list of the intellectual enemies of mankind, among those personages who should be starred with black daggers in the book of history for falsely directing, and thus retarding, the development of human thought. Historians have long since charged Plato with economic and political bias in the development of his philosophy; they have traced to his Idealism some of the major elements in late Roman and Medieval times which strangled intellectual inquiry and fostered the spiritual development and mental stagnation of the Dark Ages; they have pointed to the Renaissance and the succeeding centuries, when modern science was born and developed, as a period during which Platonism was driven out of one field after another. They assume that today we are reasonably free of its philosophic aberrations. In this last I think they are in error. Determinism applies as much to the shaping of human thought as to the shaping of mountains, and we may have to wait until a new intellectual age when the mountains which we now

* Morris Herzstein Lecture (III) delivered at the University of California, December 6, 1946. The first of these lectures appeared in the April 1947 issue of the Bulletin.

know are worn away before we shall be wholly free of those distortions in our thoughts which are traceable to this Athenian aristocrat.

Determinism applies also to the making of men, and Plato was a product of his environment, of local circumstances, and of his innate constitution. "I thank God," he said, "that I was born a Greek and not a barbarian, freeman and not slave, man and not woman; but above all, that I was born in the Age of Socrates." Here are the keynotes to his philosophy, the philosophy of an aristocrat, a snob, a bigot, and of a man with limited perspective.

Long before his time the land of Greece had suffered the troublous transition from a primitive tribal culture, characterized by inherited family privileges, to a loose conglomeration of city-states grown rich with vulgar commerce and ever seeking new and more profitable adventures. Trade had produced great personal wealth and this wealth had sought safety in reinvestment in the land until private property had become the foundation of social distinction, of the new oligarchy of rich and poor, aristocrats and commoners, freemen and slaves. It was in this turmoil between the old and the new that Socrates was hailed to trial by the democrats and condemned to death on the charge that he had been aiding and abetting the aristocratic Thirty.

Plato, born an aristocrat, hated the democrats before Socrates' death, and after this tragedy he was fired with bitterness and driven into philosophy as the only politically safe way in which to pay off the vulgar horde. He thereafter devoted himself to the discovery of that special kind of "truth" or "justice"—the two were essentially synonymous in an age when the only standard of reference was politics—which would protect aristocratic interests. Truth for Plato was identified with tradition, with inherited lands and privileges, with stability and unchangeableness, with divine decree that transcended the individual; truth was the antithesis of individuality as well as of change, of all the hated democratic forces that worked like ferments in the mob of sailors, ship-owners, traders, money-lenders, wheat speculators, adventurers, slaves, to keep them in a perpetual state of turbulence and revolution. Democracy not only placed the individual on a pedestal but it defended the very rightness of change as a natural and just phenomenon. Plato despised democracy because in fact and in principle it threatened the security of his aristocratic privileges, and in the end he rhetorically annihilated it, and all possibility of its existence, by philosophic decree.

He argued that since change is the denial of the unchangeable, the absolute, and since only the unchanging and absolute can be either knowable or true, that which changes is untrue, a half-truth, an illusion of the senses.

The *physiologi*, Thales, Anaxagoras, Heraclitus, Democritus, had asserted that what truly exists is matter which contains within itself all the laws necessary to its existence and operation, and all else is but flux and movement of atoms. These persons Plato classed with the damnable democrats, the defenders of flux, under the most scathing term he could think of—*materialists* who ignorantly took as real the objects of the world as they appeared to be, and falsely presumed to find in change and process something that is both knowable and significant. Thus developed his philosophy—since what is true must always be true, truth is absolute and eternal; the unchanging and unchangeable is the only reality, and all that deviates from it is the product of error.

Thus he built his philosophy of the Ideal with the aid of the Pythagorean theory that only numbers are real, and with the aid of the Pythagorean term, Idea, or the essence of things. To cite the oft-quoted example, a particular circle is drawn by hand and proves to be slightly eccentric, so it is erased and another circle is drawn, and another, and still another, no one of them ever perfect, no one of them indestructible, no one of them to last forever. But the archetype of the circle, call it perfect circularity if you will, was there before the hand attempted the first imperfect circle and will survive after the last imperfect circle has been erased. It alone is real. And so it is that all particular objects of whatever kind approach in greater or lesser degree some Ideal or universal. The Ideal circle is not inherent in the substantive circle which we draw, but in the mind; but not in my mind or yours, or of any particular man, for particular men come and go; since the Ideal circle endures everywhere and forever, it must be inherent in some universal, unchanging mind, which can only be the mind of God.

The world, which to our naive view appears to be made of substantive things, is, according to Plato's argument, but a shadow-show of half-truths: its particular circles, its particular men and cities and laws, indeed its particular apples and catfish and billygoats, come and go, all of them but imperfect images of the perfect and eternal Ideas of the divine mind. The Ideal billygoat (or its mathematical counterpart) existed in the divine mind before the first actual billygoat was, or smelled,

and will continue to exist and smell when the last actual billygoat, imperfect in form and odor, has ceased to be. If the democrats, the defenders of the individual, of change, of conflict, of revolution, thought for one moment that they, too, might be an Ideal in the mind of Zeus, an ultimate to which they approximated however imperfectly, they stood convicted of a vulgar and unphilosophic error—nothing that suffered change or conflict or revolution could exist in the divine mind and therefore it could not be true.

It has been said of Aristotle, Plato's pupil, that he loved his master but that he loved truth more. He forthrightly denied Plato's doctrine of the Ideal. He believed that reality consisted of particular things, and not of universals; he accepted that change and process were as much a part of nature as fixity, and indeed he doubted the existence of the absolute. The world of philosophy has ever since been divided between Plato and Aristotle, and indeed Coleridge said that men are born either Platonists or Aristotelians. From the days of the Academy philosophers have continued to wrestle with the opposition between the Platonic universal, representing what we may call the philosophic norm, and the Aristotelian thing as is. The Christian church inherited Platonism largely through Neo-Platonism, and biology inherited Platonism largely through the Christian church.

Platonic Idealism intrudes itself into our thinking whenever we use the term "normal," since the word implies both perfection and pre-determined plan. It also implies some measure of stability, for a standard of reference ceases to have meaning if it is never twice the same. It implies a pattern or paradigm which exists apart from things themselves, since we sense that perfection is not to be found in any one individual but can only be approximated to by abstraction from a relatively large group.

Biology has both historic and factual warrant for conceiving the normal as uniquely stable. It was recognized long before Aristotle that in each species of animals and plants one can perceive a type which is reproduced generation after generation. Indeed, our grandfathers adhered so strongly to this doctrine that they believed that God had created all animal and vegetable species according to type in the year 4004 B.C., after which Adam had named them, and that they had remained unvaryingly true to type ever since. Post-Darwinian biologists recognize that Bishop Usher was wrong in his calculation and that our

grandfathers were wrong in their faith, that specific types had actually come into existence hundreds of thousands, some of them hundreds of millions of years ago. Yet the extension of geologic ages serves only to emphasize that this stability of type is one of the most emphatic facts in nature—it is change in type that is so infrequent as to seem miraculous. Certainly we are tempted to believe that nature has a template upon which she patterns every starfish, every oyster, every man, and it is in large measure this stability which imbues us, as it imbued Plato, with a strong sense of the absolute in our use of the word “normal.”

Yet we perceive that within each species individuals are not all identical, but deviate above and below a mean in every character. We point to the influences of environment on development, or to the chromosomal mechanism of reproduction, and infer that during reproduction or development this or that little accident occurred, and consequently one little starfish is a little longer in the legs than another. The “normal” starfish would be one escaping all such accidents, it would perhaps represent the Ideal template.

It required the *Origin of Species* to liberate biology from the absolute, the unchanging, which was the essence of Platonic-Christian theology. The thesis of the *Origin* was biological variation, for it was on the observed data of biological variation that Darwin laid the foundations of evolution, and Mendel the foundation of genetics. Biological variation is the antithesis of both the Platonic Ideal and the stable Norm since a variable absolute is by definition a contradiction of terms—nonsense. Yet we still quite generally fail to recognize this fact. Striving for specious simplicity we tend to exclude variation from our thinking, either by ignoring its existence or by mathematically compressing it into a rigid, artificial mold. We tabulate the anatomical and physiological dimensions of our fellow mortals and, after averaging them, we correct them to what we call “ideal man,” never blushing that we know nothing about “ideal man” except that he has a body surface of 1.73 square meters and an ideal basal metabolic rate of some 40 calories per square meter per hour. We measure his cardiac output, his respiration, many functions of his glands and kidneys, and even of his psyche, and in our tables we presumptuously apply a correction factor to women to bring them up to the male’s ideal measurements, without asking ourselves, Whence comes this creature of statistical perfection, this paradigm, this prototype, to whom we approximate real men (and women) by an

easy mathematical correction?

It is clear that the attributes of "ideal man" are but a collection of mathematical averages of various features which are subject to biological variation. An average value is not only a most useful one, but almost necessary to our thinking. It presents us a single concept, easily pictured and easily remembered, which we can convey to others or otherwise shape into a useful ideological tool. We could scarcely form any clear conception as to the duration of human life from observing a hundred thousand individuals, unless by taking the average; or form any idea of their adult height, weight or other vital statistics unless we reduce the pertinent data to convenient categories and thus learn what averages and ranges are to be expected. It has been said that the whole of statistics depends upon the use of such averages.

There is, of course, the other application of averages that is equally important: ten authorities estimate the magnitude of some measurable matter, or one authority makes ten estimates, and many or all of the results differ slightly from each other; if we have no reason to attach greater weight to one result than to another, experience shows us that the average of all the estimates is more likely to be right than any other value. In this usage, the average of mensuration, the mean represents a thing actually existing, and the more carefully the mean is derived the closer our concept comes to the reality; whereas in the first usage, the average of biological variation, the mean represents something that is non-existent, a mere product of our imagination, and the more carefully it is derived the more removed it is from reality, in that there is less probability of its being identified with any one individual. And for us as Aristotelians it is the individual that counts.

If we measure a large number of individuals in a given population, we find that the variations in this or that feature tend to distribute themselves above and below the mean, between certain minimal and maximal limits, in a characteristic manner. We conventionally divide the variable into equal categories and count the number of individuals in each category: when the frequency in each category is plotted against the size of the category we obtain what is called a frequency distribution curve which, in the "normal" form, is a symmetrical structure of some beauty (Figure 1). This frequency distribution curve reveals at a glance the dispersion of the variable under consideration and affords us a description of the entire population, and thus takes cognizance of

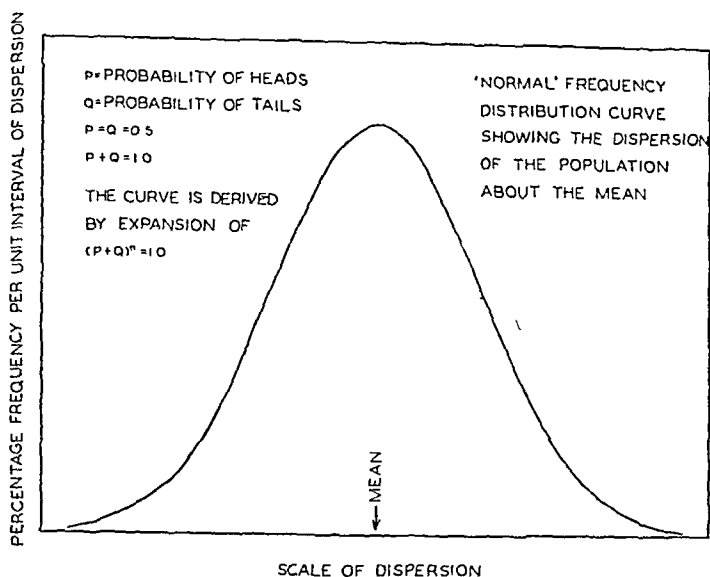


Fig. 1

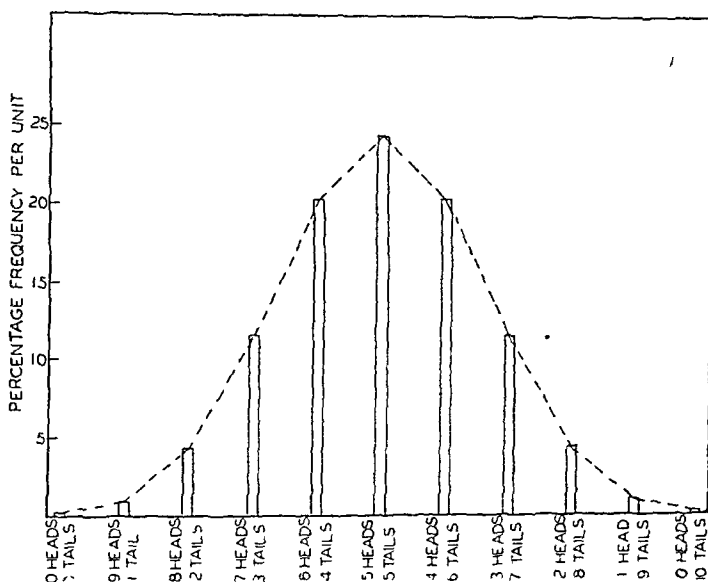


Fig. 2.

biological variation as a fact.

Because of the way our textbooks are written, this frequency distribution curve is often associated in the student's mind with errors of measurement—the terms probable error and standard error, and the use of the standard deviation, σ , as an index of the magnitude of error, constantly drives home this application. If any of us were to set a student to measuring the height of one of his colleagues and his error extended

over the range of 4 feet 9 inches to 6 feet 3 inches, we would at once stop all measurement. The term error early became attached to the curve in connection with the development of the theory of error in measurement, and here it has stuck to the misfortune of the student of biology who is thereby befuddled as to the curve's more important meaning. He fails to see it for what it is, a graphical epitome of nature, a cabalistic symbol of her compounded mysteries.

The curve presented in this figure is the so-called "normal" frequency distribution curve derived from the $p:q$ formula applicable to the tossing of pennies for heads or tails. I need not labor you with the elementary facts that a penny has only two faces, heads or tails; that it is practically impossible for it to come to rest on its edge after descending on a hard surface, and that, assuming symmetry, the chance of its coming up heads or p , is precisely equal to the chance of its coming up tails or q , i. e., $p = q$. This equation merely says that we know of no natural or supernatural force that will influence pennies in midair in the way of favoring heads or tails; and that we can discover nothing of that kind for the simple reason that the equation always works when we test it exhaustively. For all we know there may be all sorts of gods and demons struggling amongst themselves to get heads or tails, but if we toss the penny often enough we end up with the fiends evenly matched. Or perhaps because the mass of a penny is so great, these supernatural beings, currently allowed to operate only through the Heisenberg principle of uncertainty, are unable to turn it in its fall. Anyway, we learn from experience that $p = q$, and, of course, $p + q = 1$, denoting that heads plus tails equals all the probabilities there are, unless a penny rolls off the table and gets lost, when $p + q = 0$. Were we tossing pennies so constructed that if a particular penny fell heads, one or more other pennies would as a consequence have to fall heads, pure chance would no longer operate and the frequency distribution curve could have almost any and every shape.

From these two equations it is simply a matter of algebra to derive the unsmoothed frequency distribution curve (Figure 2) showing the chances of getting any combination of heads or tails when ten pennies are thrown simultaneously and in such a manner that they will not influence each other's destiny. The symmetry of the curve stems from the fact that no one event (i.e., heads in a particular penny) influences or is influenced by any other event (i.e., heads or tails in any other

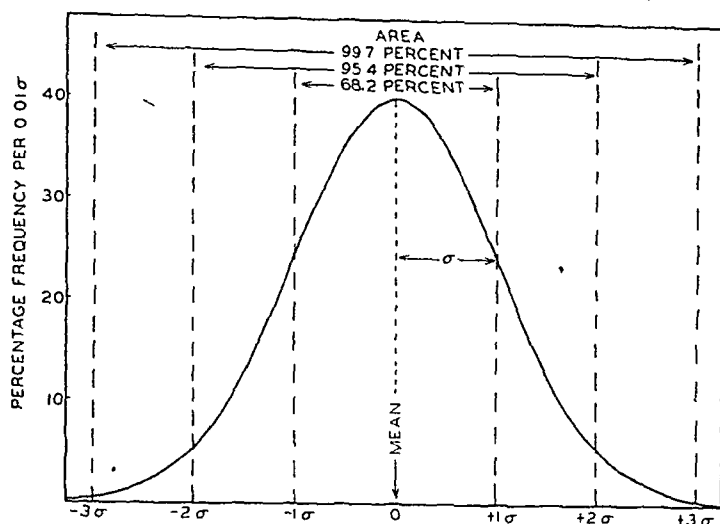


Fig. 3

penny). Hence the curve is also called the curve of independent variation, i.e., each penny comes up heads or tails independently of every other penny. The destiny of every penny is a matter of "pure chance." Why the theory-of-probability experts call the "pure chance" curve the "normal" curve is obscure, unless it is to absolve penny-tossing of any implication of demonic influence.

In the normal or theoretic curve (Figure 3), the mean, the mode and the median coincide, and the range theoretically extends from zero to infinity. In practice, frequency distribution curves rarely achieve the perfect symmetry of the normal curve and the range always extends between some minimal and some maximal finite value. The curve may, however, be narrow or wide. The normal curve has its own internal measuring rod: this is the distance from the mean to the point of inflection of the ascending or descending limbs, which affords a convenient measure of the median range, or the degree of dispersion, of the variable under consideration. This distance is well known to you under the name of σ . The structure of the curve is such that 1σ to either side of the mean will include 68.2 per cent of the population, $\pm 2\sigma$, 95.4 per cent, $\pm 3\sigma$, 99.7 per cent.

Where is the normal in relation to this curve? We cannot identify the normal with the mean for the mean is a mere mathematical abstraction not possessed in any sense by any individual in the population. Nor can we identify the mode as normal merely because the population

density is greatest at that point, nor yet the median, merely because this point stands in the middle counting from left to right. We may arbitrarily assign the normal to a band encompassing a substantial fraction of the population above and below the mean, but shall we draw this band at $\pm 1\sigma$ from the mean, to include 68.2 per cent of the population, at $\pm 2\sigma$ to include 95.4 per cent, or at $\pm 3\sigma$ to include 99.7 per cent? Clearly nothing about the curve itself will aid us in making this decision. All we can say is that at $\pm 1\sigma$, $\pm 2\sigma$, $\pm 3\sigma$ from the mean, the chances are 1 in 3, or 1 in 20, or 1 in 300, that a given individual behaves consistently with the presumptively homogeneous population from which our curve in the first instance is derived. In erecting the curve we assume that all the individuals whom we tally therein are "normal," in the same sense that we assume that all 10 of our pennies are normal. If the term normal is used at all in reference to the normal frequency distribution curve, it must include the entire range from the lowest to the highest value, the entire population must be considered normal. This definition of normal is admittedly not very useful.

But, you say, this curve is as much a mathematical abstraction as the mean itself; it differs from the mean only by having two dimensions, magnitude and frequency, instead of the single dimension, magnitude. And where is the *thing* in itself, the individual, which Thales, Anaxagoras, Heraclitus, Democritus and Aristotle, accepted as the proper subject of philosophic and scientific study? With this criticism I agree. As Aristotelians we must base our thinking upon actual and material things with three dimensions. For that reason I beg permission to include in this discussion one who conceived as flesh and blood will stand in vivid and realistic contrast to such abstractions as the population, the mean, median, and standard deviation, one who by her actual dimensions as by her admirable qualities and pleasing personality will impress us with the importance of the individual. I refer, of course, to our old friend, Clementine, whom we all recall from early, happy days.

There are some who, because of the almost pernicious accident of rhyme between her name and the size of her shoes, will remember her first on this account, but there are others, I am sure, whose minds are less inclined towards sardonic trivialities, who will recall that it was in the beautiful state of California,

*In a cavern, in a canyon,
Excavating for a mine*

*Dwelt a miner, forty-niner
And his daughter, Clementine.*

As Aristotelians we have agreed that it is the substantive things of life, the specific objects with mass and size and color, particular persons whom we know, that supply the proper data for scientific inquiry and philosophy. But biological variation is also a fact, and without the background of a frequency distribution curve a single individual is only an unrelated episode, an unintegrated experience. Perspective requires that in our search for the meaning of normal the individual must be assessed in proper relation to the total population of which he or she is a member. Only thus can we render our judgments in impersonal terms, and not in the manner in which we judge, let us say, a favorite melody, that which is entwined with our memory of Clementine, or any other. And thus must one who is conceived by those who remember her as normal in nearly all, if not all respects, be viewed lest we fall into that deceptive enchantment which distance, time or personal predilection cast upon our unwary faculties. If there seems to be something heartless in my coldly analytic attitude, in my insistence that Clementine, who in our memories approaches the ideal, be judged by comparison with mortals, it is not because I lack affection or loyalty, but because these are not the instruments by which we will achieve our goal.

The all-important data, the so-called vital statistics, are things that we rarely gather about our friends. From some perversity in human nature we accumulate fewer vital statistics about our friends than about our enemies. I am in the unfortunate position of not having at my command all the vital statistics that I would we possessed about Clementine. For such facts as I do possess I am indebted to Mr. Percy Montrose, who reduced them to immortal verse in 1884. Mr. Montrose, I regret to say, has apparently been lost to history, a diligent search having failed to disclose his origin or his end. But the charm of his meter and rhyme, if I may venture so bold a metaphor, are of a parity with the charm of the young lady whose sorry fate has stirred thousands of men to throaty and tearful song.

Although Mr. Montrose has given us many facts, I have been forced to supplement his all too brief biography by careful inquiry among mutual friends. Allowing for reasonable error, but error which I am sure will not vitiate our final judgment, I think that most of the lacunae in the documented history can be filled.

Light she was, and like a fairy,

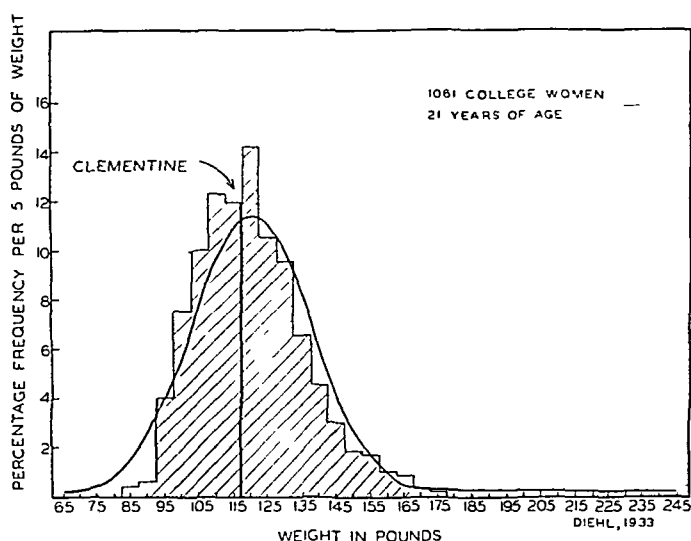


Fig. 4

is of course in part poetic extravagance on the part of her inspired biographer, and yet, perhaps not so much of an extravagance at that. I do not know Clementine's age at the time of reference, and like so many statistical data the time of reference to one detail may not be simultaneous with purportedly related data on other matters, but assuming that the impression here epitomized in a classic simile is to be taken seriously, and weighing carefully the considered assessments of my advisors, I deduce with some confidence that her weight was approximately 117 pounds at or about the age of twenty-one.

Is this—or was this—weight normal? As I have said, we must not allow either the enchantment of time or the persuasion of predilection to sway our opinion in such a matter. The only unprejudiced approach is to refer this datum on weight to the normal frequency distribution curve (Figure 4) showing the weights of females in her age group.

One thousand and sixty-one^o American college women twenty-one years of age¹ should certainly afford us a sound sample of the normal. The range in weight is from 65 to 245 pounds, a broad spread for the normal however you look at it. The mean is 120.7 pounds, but not a single woman weighed exactly that amount. The high frequency of women weighing between 95 and 122 pounds is balanced by a relatively few women of large weight, or moment, as the mathematician says, where the curve is skewed to the right. Nevertheless, the frequency distribution corresponds closely to the normal curve, indicating

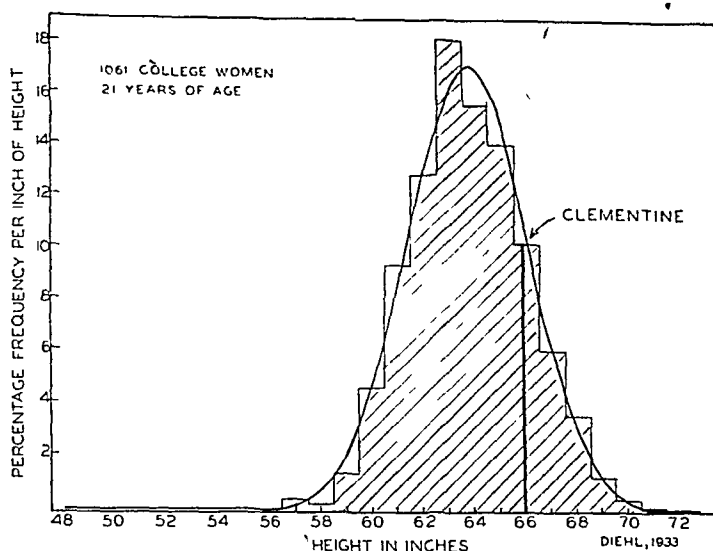


Fig. 5

that the factor or factors which make for inequality of weight in American college women largely enjoy independent variation and operate by pure chance, at least in this sense: the circumstance that one college woman is light or heavy does not influence the probable weights of her classmates. Or does it? May not the circumstance that one college woman is slender lead other college women to dietary restrictions, and thus squeeze the histogram to the left and out of the boundaries of the normal curve? We will later raise the question whether the circumstances of going to college may influence the weights of all the women who do so.

Clementine, who, in a manner of speaking, has been in every college in the United States, weighed less than the mean by 0.216σ , indicating that 83 per cent of the population can be expected to deviate from the mean more than she does. We have taken as our normal standard of reference "the weights of college women 21 years of age"—by that definition Clementine is normal in that she is consistent with the standard in respect to weight.

The question arises, however, whether it is adequate in judging normality to use only one criterion of reference, weight, so let us try a second criterion, namely, height (Figure 5). Secondary sources which I need not detail, but which when collated with other data are wholly convincing, lead me to set Clementine's height as close to 66 inches. Thus she was above the average height by 1σ , indicating that 32 per

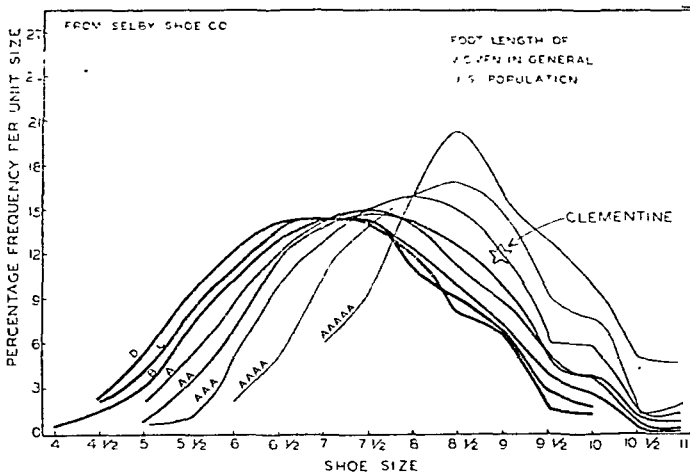


Fig. 6

cent of the population can be expected to deviate from the average height more than she does. She is still consistent with our standard of normality. The only other thing we can deduce from this additional datum is that she was slender—tall for her weight—statistics have a teasing way of proving what one already knows!

But is it abnormal to be slender? This is a matter of the correlation of two variables. Do they simultaneously enjoy independent variation, or do they tend to wax and wane together? The answer in this case is that they do not enjoy simultaneous independent variation but tend to vary in proportion to each other. Thus we are spared extreme skinniness in very tall women, and complete rotundity in very short women. The statistician, that ingenious person who is guiding us through this labyrinth, has integrated the two variables by calculating what he calls "body-build" which is equal to $\text{weight} \times 1000/h.^2$ According to this quotient, which affords quantitative, mathematical precision to what the eye can only qualitatively assess, Clementine is still consistent with being a college woman. In this case, multiplying one reasonable certainty by another has only led to a third reasonable certainty, but this manipulation of figures calls to mind that it is yet to be proved, certain physicists to the contrary, that a mathematician can get anything out of an equation that he has not put into it, other than the leisure which is made available by any labor-saving device.

Let us try a third criterion—foot size (Figure 6). It is something of a surprise that though most women's colleges measure something, and

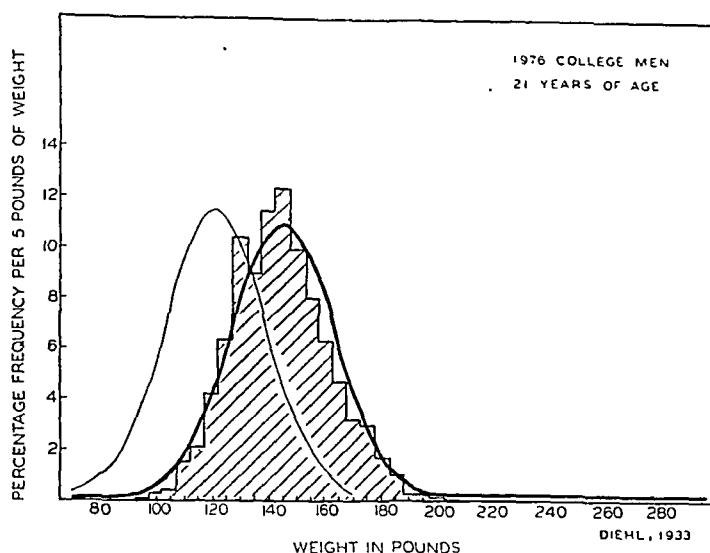


Fig. 7

many of them measure almost everything that is measurable about women, no one of them seems to have taken any interest in the size of feet. So for our standard of reference we must turn to the sizes of shoes bought by women in the general population.² The modern prejudice in favor of wearing shoes may be discounted as merely modish or even abnormal, and it is probable that shoes were rarely worn in the remote gold mining camps of California in the early '50's. However, Clementine was adverse to walking barefooted over the rocky trails, for, as Mr. Montrose tells us,

*Herring boxes, without topses
Sandals were for Clementine.*

An authority on herring boxes of that period advises me that they were of course variable in size, but generally of a width of some three inches. This datum, combined with her body build, leads me to infer that she wore a AAA shoe. The matter is, however, of slight importance—if the width of Clementine's foot did not exceed a AAAAA, she is still consistent with what we have chosen as our normal standard of reference.

It will be recalled that we initially took as our standard of normality 1061 American college women. But can we be confident of the reliability of any population of women as a normal standard of reference? Should we not examine them against a broader background before accepting them as a sample of the absolute? One method that suggests itself is to compare them with college men of the same age (Figure 7).³

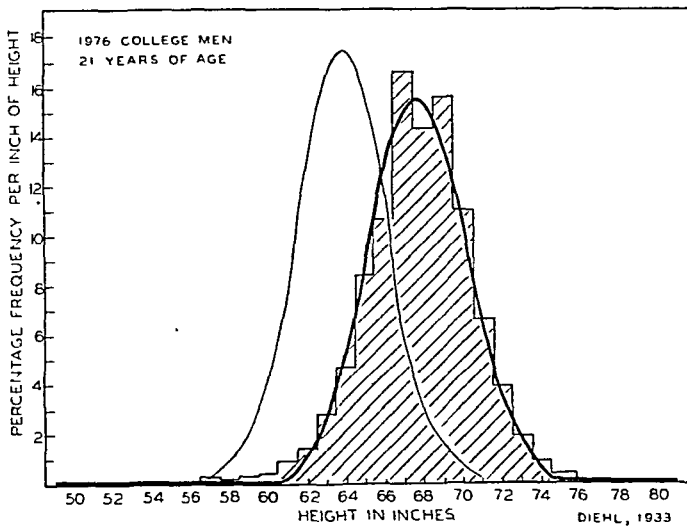


Fig. 8

The range in weight is substantially greater than among women, 68 to 298 pounds as compared with 65 to 245 pounds.³ Moreover, the frequency distribution curve for weight is somewhat wider for men than for women, i.e., the variation or dispersion about the mean is greater. The degree of variation about the mean is expressed by σ and appropriate comparison of σ for the two curves shows that women are significantly more uniform than men, they conform more closely to a hypothetical stable ideal, as they doubtless have always thought. But does this greater stability in weight make them more normal than males? There is an aphorism from the library of Assurbanipal, king of ancient Nineveh, which asks, "Does a woman conceive when a virgin, or grow fat without eating?" Voluntary dietary restriction is certainly not normal.

There are, of course, other factors operating, as is evident when we compare men with women with respect to height (Figure 8). Here again women are more stable, they show less variation about the mean. To understand how this may come about let us compare height and weight. In both sexes the variation in height is much less than in weight; height is a much more stable feature of the human body than weight. If the body were shaped roughly like an egg, its mass would increase as the cube of its height, a circumstance which itself would make for greater variation in weight than in height, even among ideal eggs. But neither men nor women can be conceived as behaving like ideal eggs; in both sexes weight is largely a matter of soft tissue which can be

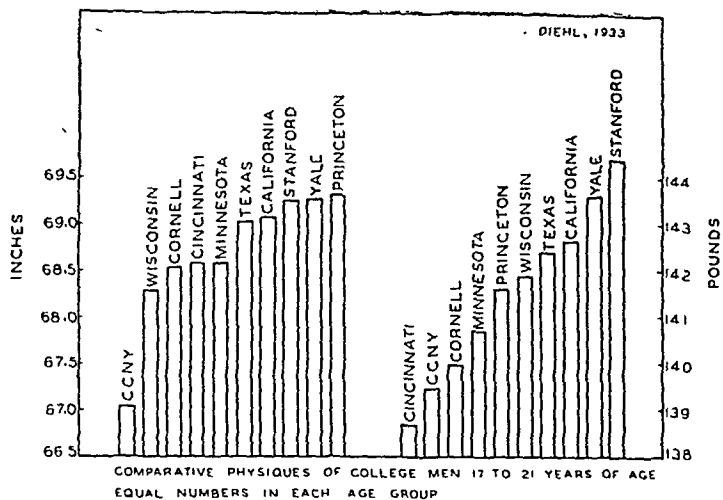


Fig. 9

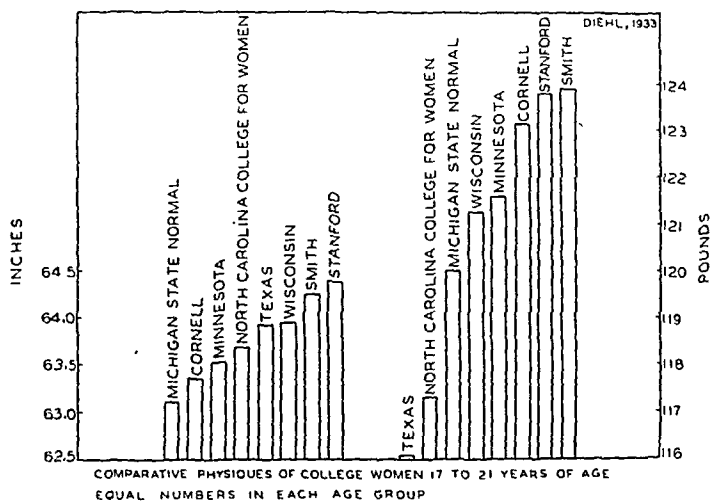


Fig. 10

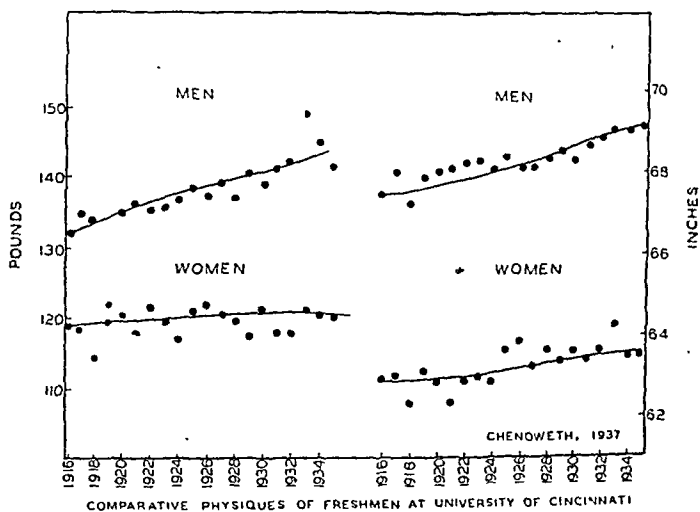


Fig. 11

added or subtracted by indulgence or hardship. Height is largely a matter of long bones and the vertebral column, the dimensions of which are less susceptible to fluctuations in dietary fortune, but are largely determined by the pituitary gland. Are women more normal than men because they agree about pituitary secretion among themselves, but disagree with men?

The question has arisen whether going to college affects the parameters under consideration. It does, in advance of matriculation. Both men and women who enter most colleges are taller and heavier than the non-collegiate general population. College women at the age of 16 average five pounds heavier and over one inch taller than their non-collegiate sisters, though they are four pounds lighter at the age of 21. Unlike women at large, college women do not increase in either weight or height between 16 and 21. It has been suggested that restriction of diet may retard their growth, but I have not observed that anyone has considered a possible causal relationship to the college diet itself, or, even less remotely, the effects of the intellectual life. Similarly college men are taller and heavier than the general population. Apparently, in the college group acceleration in development has occurred prior to the age of 16, so that by the age of 17 or 18 years they have more nearly approached full growth (Figure 9). But the situation is not the same in all colleges; among men, Stanford and California are exceeded in height only by Yale and Princeton, while in respect to weight only Yale is a competitor. C.C.N.Y. comes out short in both respects (Figure 10). Among women, Stanford comes out first in height, but in weight is beaten by an ounce by Smith. Our criterion of normal depends on what college we pick. Is this predilection of a few colleges for mass and length normal?

These general differences awaken us to a new difficulty, that of finding a stable population. Numerous studies have revealed that over the past century and even in the past few decades, there has been an acceleration of growth and maturation. In several regions menarche occurs two years earlier than a century ago, and in three American Universities the mean menarchial age has dropped by one year in the last thirty years. The average height of English soldiers has increased about 4 inches in the past century, that of American college men by about 2 inches in the last half century, that of women only slightly less (Figure 11). For several generations children have quite generally ex-

ceeded their parents (of like sex) in stature and earliness of puberty, and berth length in American sleeping cars has been repeatedly lengthened, from 71 inches (center to center of partitions) in 1859 to 77.5 inches actual mattress length in many cars now being made.^{4, 5, 6} Diet may have played a part in this acceleration and extension of growth, but some investigators⁷ relate the phenomenon to a period of reduction in the temperature of the earth, and believe that the growth and development peak may have been reached with rising temperature in the 1930's, and that future decades are likely to witness a racial recession.

We have asked ourselves to what extent can our ideal, Clementine, be conceived as approaching the normal in respect to any one of several mensurable variables. We may measure Clementine, but we have not as yet measured the normal. If the word is to have any meaning it will have to be in reference to some selected population. In the face of the above facts it is clear that we cannot lay our hands upon a stable population. On what grounds, then, can we call anything human, normal, unless we call everything human, normal?

Perhaps we have been searching in the wrong direction—perhaps the mere dimensions of things do not comprise their essence. Perhaps we should seek in the dynamic, rather than the static, to discover the normal. One of our colleagues, a neuroanatomist, has in effect already made this search in terms of function. Rejecting, as we have, the average as a mere mathematical computation, a specious name representing no reality, he defines the normal as “that which functions in accordance with its inherent design.”⁸ He suggests a simple example: if we come across a broken wheel it is possible to infer not only the inherent function of the object, but in addition what is wrong or abnormal about it. “. . . the essence of (its) design is circularity including the presence of an axis . . . (and) the function potentially associated with circularity in a discrete object is revolution.” To those who may object that we learn the relationship between circularity and rolling by experience, and therefore by the law of averages, he replies with assurance that we can recognize a broken wheel the first time we ever see one, even though we have had no other experience with wheels. In this nascent experience the thing is not a novel object of unaccustomed design and function; we are under no disability whatever to recognize either that it is a wheel, with at least the implication of rotation, or that the local departure from design which prevents the fulfillment of the wheel's natu-

ral function is to be accounted for by the circumstance that the wheel has been broken. Were this not true, he says, the first wheel could never have been either recognized or invented.

The origin of the wheel is wholly obscure. Whether it was discovered by a perspicacious inventor who shared with our author this inborn insight into the relationship between design and function, or by a comparatively stupid dunce who fell upon the idea by slipping on a round stone or log, i.e., by the law of averages, I do not know. But I do not think that to define normal as the relationship between design and function is going to get us far. If it is normal for an intact wheel to roll in accordance with its design, is it not equally normal for a broken one to fail to roll, in accordance with *its* design? And why must a wheel roll, anyway? Only a boy who wants to play hoops, only a lazy man unwilling to carry his load or to walk from place to place, or who finds in the relationship of circularity to rotation a tempting teleological argument, would insist that a wheel must roll. Is a wheel not functioning properly when it lies flat upon the ground? Many a chipmunk thinks so. Our definition of normal must not be subordinate to human usefulness. We appear to be in a blind alley—indeed I think we are slipping backwards, for let us see to what conclusions the author's own anthropocentric argument leads him:

"We intend to assert," he says, "a direct, but largely unremarked, implication of biology, viz., that the organic design of the human being is the one complete design of its kind existing within the entire organic kingdom on this planet. The detailed arguments on which the statement rests are too lengthy for present reproduction but it is felt that almost any biologist must agree with them upon reflection. They are based not only upon structural considerations but on functional ones as well; no other creature behaviorally manifests the integration of intellectual, affective, and sensori-motor response which characterizes man or, if any do, then by no means to the same degree of completeness. Thus the human design represents the complete and fundamental organic pattern from which other species depart by one degree or another, and the basic paradic [= normal] of the organic kingdom is the anthropadic. . . . On the basis of completeness the anthropadic must be the ultimate paradic of the whole organic kingdom."

Oh, Clementine. . . ! How little did you suspect that you were the "paradic," the paradigm, the norm for the whole organic kingdom! But

do not be alarmed by this apotheosis. . . . These arguments are not new despite the fact that the paper I have quoted was published in the year of diminishing grace, 1945. Christian theologians, beginning with Augustine, elevated man to the cosmic dais, only they modestly recognized that man had a few minor imperfections and so under the doctrine of the Perfection of the Original Creation (prior to Adam's sin, of course, on which occasion the serpent tempted Eve (who was weak and perhaps abnormal) and Eve tempted her husband and because of Adam's sin Creation was despoiled)—because of these things they pointed to Adam, and not to Adam's progeny, as the paradigm of Creation. I would that we could do the same. I would that we had Adam—I mean no disrespect—on our dissecting table so that we could study all his "paradic" parameters, the width and breadth of his skull, the weight of his brain and heart and kidneys; I would that we could even make a few observations on his cardiac output and his renal clearances. . . . No Clementine, you are, if I may say it without being misunderstood, no Eve, and in any case, even the doctrine of Original Perfection and the legend of Adam and Eve have been heavily discounted since the publication of Mr. Darwin's book, since man has been revealed to be something less than a fallen angel and inadequate to serve as a model for the whole of organic creation. . . .

Have we, then, in our search for the normal, become lost in an endless labyrinth? Let us return to where we started, the stability of type that pervades the entire organic kingdom—it has been this stability of type coupled with the Platonic Ideal that has fostered our illusion that the word normal has any meaning. But is this stability of type real, does nature have a common template upon which she patterns every starfish, every oyster, every man? We know more about men than about oysters and starfish, and for man we can confidently answer, No. The high improbability that no two men are exactly alike in their chromosomal pattern (except in the case of identical twins) is one of the best established facts of biology. Every man differs from every other man not only in his finger prints but doubtless in a thousand other characters. If no two men are exactly alike in their chromosomal pattern, then where is the normal man?

The concept of the normal is an illusion of our own making. It is not easy to abandon one's illusions. Those who walk among the sick ask themselves many times a day, is this normal or abnormal? The

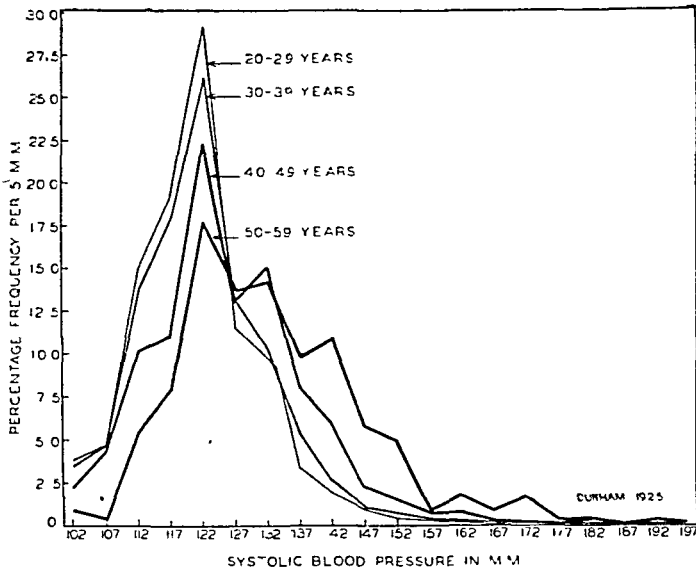


Fig. 12

physician who would prevent rather than cure disease must carry the question into that no-man's land where disease is nascent and difficultly discoverable—where does the normal end and disease begin? We are engaged in an issue between life and death and we cannot define our enemy—what is disease? Is it not normal for some men to be infected with non-pathogenic pneumococci—do we not call it abnormal only when the organism is pathogenic? But do we gain anything thereby? What does it aid us to define pneumonia as abnormal when we are not embarrassed to think that a pneumococcus is a normal organism that follows a normal course of reproduction in somebody's alveoli, to the victim's inevitable distress and until he dies—unless treated with sulfanilamide—all in accordance with laws apparently as unchanging as Plato's universals, the whole a normal sequence of events? Is it not normal for a diabetic to exhibit glycosuria, for a cretin to be just what a cretin is, for a malignant tumor to do just what a malignant tumor does, for a schizophrenic to behave like a schizophrenic?

Let us take one more example of a physiological variable where we habitually use the word normal—blood pressure (Figure 12). Where will we set the limits of normal blood pressure? To do this in an arbitrary manner would be not only intellectually dishonest, but dangerous, for these blood pressure frequency distribution curves are charged with pain, disability and death. . . .

Is it not true that we are concerned, not with the preservation of tradition or of aristocratic rights, or with the apotheosis of an Ideal blood pressure, but with these brute facts—pain, disability and death? And are there not many ostensibly normal circumstances that lead to pain, disability and death? Senescence is normal—I doubt that any biologist will deny it—and childbirth is normal, and between birth and senescence it is impossible to define disease except in these terms—pain, disability and death.

Our task is to ameliorate pain, to relieve disability and to postpone death by reading the future in the present constellation of events, in the hope of modifying future events. Whether we choose to call any particular constellation of events normal or abnormal is not of the slightest significance. That we have in some measure been successful in our task of avoiding pain, disability and death is partly attributable to our great theory of disease, stemming largely from Cohnheim, namely, that singular, particular causes underlie disease. If a man has pneumonia, it is because a specific noxious agent has invaded his body and made headway against his defenses. And so with the deficiency diseases, resulting from the absence from the body of particular, necessary elements; and here, too, one can place malignancy: particular body cells, perhaps only one cell in the beginning, have escaped from control and by accelerated development and overgrowth destroyed vital organs. And here, too, one can place many inheritable diseases, as well as established predispositions to disease—modern genetics permits us to believe that in all such cases a particular fault in one or a few chromosomes may be responsible.

Under this particularistic theory it has been relatively easy to slip into the error of dividing everything into the normal and abnormal. But as opposed to or supplementing a theory which looks always for simple causes (and is confirmed by always finding them complex), is it not conceivable that there can be disease which may not be so particularistic in its genesis, nor yet necessarily inheritable? Suppose we examine the frequency distribution of a well shuffled pack of fifty-two cards. There are only four chances in 635,013,559,600 of being dealt thirteen cards of one suit, and yet when such a hand falls upon the table it falls in accordance with all the rules that govern the fall of cards in a common or modal hand. It is as much a normal hand as any other, even though a very rare one. Suppose those fifty-two cards were so many chromosomal determinants of somatic characters, none of which is very

obvious or very important in itself; but suppose that in rare combinations, like thirteen cards of one suit, they spelled jeopardy for the unlucky player. The organism is in perpetual conflict with its environment and what is one man's environment may be another man's ruin. It has been said that God must love the common man because he made so many of them: may we not suspect that there are more individuals at the mode of biological variation because they are better fitted to survive in a specified environment than are the individuals at either extreme of the range? The man who gets too many of any one suit in his genetic makeup may be destined for an early death because of his inability to cope with the stress of his environment. Yet by all the rules he has had a normal deal. His obscure pathology need not be inherited by his children, nor could one point to a particularistic cause such as pneumococcus, a vitamin deficiency, a tumor or a default in some particular gland, as the primary cause of his distress. Can we name such diseases? Perhaps senescence is such a disease, a matter of too many, or too few clubs. Perhaps there are others. Perhaps we have looked so hard for particularistic causes under Cohnheim's influence that we have found them where they do not exist. Perhaps by classifying everything as normal or abnormal under Plato's influence we have overlooked other possibilities. Perhaps the pathologist should take the theory of probability into his laboratory and apply it to ostensibly normal people.

And there's that word again. The Platonic Ideal lives on in our Aristotelian house of science, a formless, limitless, insubstantial ghost not to be captured by any trap set by the anatomist, physiologist or statistician. There is no such thing as an ostensibly normal person—only persons who show no ostensible danger of pain, disability or death. The word normal is useful in only one sense—as a tag for ignorance.

It is a paradox that when probability came into philosophy, freedom was expelled. Causality took over our lives and our innermost thinking, and even disease and death were constrained to run a deterministic course. Environment, circumstance, and constitution—these three became our Fates. No better example could be adduced than that tragedy, reference to which I have hitherto avoided: as Mr. Montrose recounts of Clementine, in the manner of those who depend for their sustenance on Nature's bounty and who must discharge their obligations to Nature's creatures promptly and regularly,

*Drove she ducklings to the water
Every morning just at nine,*

Here, in environment and circumstance, was the fatal pattern laid. Though I cannot exclude the possibility that constitution in the matter of her foot and footwear accelerated the mischance, when there is sufficient repetition probability becomes dead certainty, and one morning Clementine

*Hit her foot against a splinter
Fell into the foaming brine.*

I am sorry that at this point I must interject a harsh note of criticism of our biographer for committing a solecism as indefensible as it is shocking. Fully recognizing the demands of meter and rhyme in poetic form, and appreciating the difficulties of discovering another noun adequate in respect to both context and euphony, I fail to understand how Mr. Percy Montrose could have penned that iambic tetrameter. That the cool rivulets of condensed cloud trickling between mossy stones high on the Sierra Nevada, the springs which well forth from canyon wall or glacier's lip, the gurgling brooks and torrential streams which tumble and toss down the deep-hewn, shadowed gorges of California's mountains—that any one of these crystal cataracts should be called *brine* is an offence against truth and taste from which I cannot recover.

I would also like to place on record my conviction that the sixth and seventh verses, commonly appended at the end of the musical score as though to conserve space, are in truth removed from the manuscript proper for a better reason. Careful study of internal evidences convinces me that these verses, the one relating the death from sorrow of Clementine's father, and the one starting "In my dreams she still doth haunt me," are in fact spurious, apocryphal forgeries by a later hand attempting to imitate Mr. Montrose's rhythm, but rendered indelicate by too many trips to the beer keg. And I may also note that, according to my authentic record, in the last bar of the chorus the melody does not follow the frequently heard (if not inharmonious) course from C to E, but repeats high C precisely in the manner of the verse.

But these details are unimportant. My point is that, not in the normal or abnormal, but in environment, circumstance and constitution is concealed our potential fate, and each of these is complexly manifold and complexly changing. Against the potentialities of fate we must oppose calculated action.

*Ruby lips above the water,
Blowing bubbles soft and fine,*

*A-las, for me! I was no swimmer,
So I lost my Clementine.*

We must abandon our dream of the absolute, the unchanging, which began when Pythagoras created the world of eternal numbers, and Plato of eternal Ideas. It is required of us that we find that which is significant not in the absolute, but in diversity and change and transmutation.

*In a churchyard, near the canyon,
Where the myrtle doth entwine,
There grows roses and other posies,
Fertilized by Clementine.*

Our search for the Ideal, the paradigm, the pattern of perfection, has led us only to disillusionment because that which we seek is but the product of our dreams. The normal is gone because it never was.

*O my darling, O my darling,
O my darling Clementine,
You are lost and gone forever,
Drefffal sorry, Clementine.*

If we cherish the Ideal the more because we cannot attain it, because nature has never attained it, this poignant craving but serves to fire us with greater zeal and fidelity to our proper companion in philosophy, the substantive, despite her imperfections and the fact that she is never twice the same. Some modern but unknown philosopher has captured the nuance of the Platonic-Aristotelian transformation in a quatrain which perhaps you know, and love:

*How I missed her, how I missed her,
How I missed my Clementine,
'Til I kissed her little sister,
And forgot dear Clementine.*

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BULLETIN OF
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PROPHYLAXIS OF CANCER *

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At this time in the history of the world, when mass psychology is geared to the belief that *any* problem of science can readily be solved if enough money and brains are thrown into the project, the solution of the riddle of cancer seems painfully slow and laggard. A superficial examination, based only on actual end-results, would indicate that our present knowledge of the causes of cancer, its effective prophylaxis, and the cure of patients with the disease, is still meagre and at a low level. This does not hold true, however, if we scrutinize the picture more closely, for we will then find that real progress has been, and is being made in the three fields of cause, prevention, and cure.

We have gone a long way in furthering our knowledge of the cause of *many* types of cancer; a long way on the road of prevention of certain types of cancer; and a long way toward improving the results of therapy in a few types of human cancer. As our knowledge and skill increase, further improvements in our efforts toward prevention and cure are slowly being brought about. Progress is being made in each of the three fields. It may be profitable to be dissatisfied with our *rate* of progress, but we must not be discouraged. An atom bomb-

* Address before the 19th Graduate Fortnight of The New York Academy of Medicine, October 18, 1946.

conscious public, fed on spectacular accounts of scientific achievements, is naturally impatient for a miracle in the conquest of cancer, but we do not look for any over night solution.

The problem of the prevention of cancer is fundamentally linked to the *cause* of cancer. There are many factors tied up in the cause which must here receive collateral consideration; for it is the collateral factors which give us the opportunity to introduce prevention.

In general, there are two basic attributes in the production of a cancer. First, the *intrinsic factor*: that is, those elements which are inherent within the cell itself; and secondly, there are the *extrinsic factors*, or the environment of the cell, which influence cell life and growth. In the latter lie our main opportunities to prevent cancer, as we can frequently change the environment of the cell.

You may ask, "What is prophylaxis of cancer?"

Prophylaxis is the detection and the correction of conditions under which cancer is known to arise; and the treatment of lesions which we recognize will eventuate in cancer.

In a consideration of the *intrinsic factors*, one must give thought to heredity. Cohnheim's theory of the inclusion rest also belongs here. Von Recklinghausen's disease and one of its frequent concomitants, neurogenic sarcoma; hairy pigmented nevi, and even melanoma, should be considered as the result of intrinsic factors. On the other hand, the rarity of cancer of the cervix in the Jewish woman is probably due not so much to the heredity factor of the race itself, as it is to the absence of local chemical changes and bacterial putrefaction in a race that practices the religious rite of circumcision.

A perfect example of the *intrinsic* factor produced by an outside agent is that experiment of Little and Bagg, who radiated the germ plasm of mice. By this external agent they were able, after several generations, to produce litters having only one kidney, having webbed toes, etc., indicating that certain chromosomes and genes were modified by the *external* agent, even though it was the *intrinsic* factor which is chiefly manifested in inheritance.

On the other hand, the environmental, or extrinsic, factors bring us to an exact consideration of the hazards of chronic irritation, of virus-like bodies, of hormones, of avitaminosis, of the insults of actinic rays and radioactive rays, of carcinogenic chemicals, of thermal, mechanical and parasitic trauma, in the production of cancer. A new

opportunity for a practical approach to changing the environmental hazards leading up to cancer is being afforded through the annual physical examination of so-called well persons, and through the cancer prevention clinics and centers, a recent development in American medicine.

The reluctance of the average American to go to his family doctor for an annual physical check-up is well known. His attitude is: "Why should I go for such an examination when I am feeling perfectly well?" The attempts of organized medicine, such as the American Medical Association and the American College of Surgeons, to get people to safeguard themselves by such examinations, have not met with the response we had hoped. However, the efforts of the American Cancer Society to educate the public by way of the radio, lectures, and the press, have apparently succeeded in creating a nation-wide demand for such a service as prevention or detection clinics. And it is to the family doctor, as well as to these cancer prevention clinics, that we must chiefly look if we are to increase the scope of prevention of cancer.

Skin: 1. Some years ago at the International Cancer Conference in Madrid, the late Dr. Ewing went to great lengths to point out the deleterious effects of excessive doses of sunshine in the production of skin cancer. It is my opinion that sunburn in the young is not nearly so important as sunburn in those past middle age and in those who have aging skin. Skin subjected to large amounts of actinic rays during the summer too frequently is presented to the doctor in the fall, covered with precancerous lesions, such as epithelial papillomata, verrucae, and pigmented nevi. I well remember a Columbia professor who was extremely fond of sunshine in excessive doses. One winter he spent two weeks in Florida, where he carried out his annual sun ritual. On his return to New York, I saw him and found an acute cancer of almost the entire lower lip.

The development of basal cell cancers on the forehead, nose and lip is common in those golfers who spend hours in the sun bareheaded. Likewise among fishermen, even when they wear head covering, but who get excessive actinic rays from the reflection of the sun on the water.

The removal of all precancerous lesions of the skin will save many a life from cancer, as skin cancer is the easiest of all types to cure.

2. Anyone who has ever had even a single dose of low voltage

x-ray applied to the skin is a possible candidate for subsequent skin cancer. Atrophy of the oil glands and of the skin begins with the x-ray treatment and its resultant x-ray dermatitis. Hayes E. Martin has made an interesting study of skin cancers resulting from x-ray therapy, especially in that group of women who received x-ray treatment for the removal of superfluous facial hair. It is significant that many develop cancers of the skin a number of years later—as late as 20 years subsequently; and some even after only one x-ray treatment. X-rays or radium applied to human skin has far greater danger than is generally recognized even by the great majority of the medical profession.

3. A melanoma, either black or non-pigmented, should be surgically removed before the opportunity for mechanical insult, infection, or razor cut, is presented. And incidentally, anyone with a large experience in melanomas is impressed with the inadequacy of dealing with the problem of total excision by the use of the electro-surgical needle—by desiccation. In doing a surgical excision, make it a rule to go wide of the melanoma, and as deep into the tissues beneath as one goes wide of it. A practical rule of value is to excise those skin lesions which are unquestionably of black pigment, and leave alone those which are brown. The exceptions to this rule are the epithelial papillomata, which are black due to the accumulation of dirt in the interstices of the projecting papillomata. A practical differentiation in diagnosis has been brought out by Pack who scrubs the lesion with soap and water. By so doing, the lesion becomes white if it is a true epithelial papilloma, and remains black, if a melanoma.

4. Every large skin burn which does not heal properly should be grafted. The prevention of cancer in burn scars is nearly 100 per cent possible if grafting is done at the correct time. Radiated lupus, if suspicious, should be grafted. With the development of arsenical dermatitis, excision of damaged areas and grafting are imperative, and this also applies to kraurosis vulvae.

5. Workers in gas service stations and oil plants have presented a new group of skin cancers of the hand. This occupational disease is caused by neglect of the workers to scrub the tar, oil and gasoline from the dorsum of the hand, where they remain as irritating chemicals, frequently producing skin cancer.

Thyroid: As has been pointed out by Lahey, thyroid cancers frequently begin in the thyroid adenoma. Removal of the adenoma leaves

little opportunity for the subsequent development of a thyroid cancer.

Breast: 1. Fibroadenomata occur in young women, and make their first appearance during and after the development of the breast, at puberty, approximately from 13 to 18 years of age. It is well to remove them, as they may rarely become the seat of either a carcinoma or a sarcoma, depending on which element, epithelial or fibrous, takes on malignant characteristics. Only an extremely small percentage, however, become malignant. It so happened that the last case Dr. Ewing and I had together was that of a young woman of 29 years, who had a "carcinoma simplex" develop in a fibroadenoma. Since writing this article, I was much surprised to find that Grantley Taylor of Boston, a previous speaker on this Graduate Fortnight, stated definitely here that fibroadenomata never become malignant. This viewpoint is contrary to the monumental work of Gross, and most modern pathologists.

2. The papilloma has always been considered a precancerous lesion of the breast, and the practice has grown up about this lesion of performing a simple mastectomy as a prophylactic measure. I deplore this treatment, and consider the proper way to handle the lesion is to excise it locally. Of course, the great difficulty lies in one's ability to find the lesion, whose presence is called to our attention by blood, or lemon-yellow or clear serum emerging from one of the 20 ducts of the nipple.

If one takes great care and time, he will usually find the papilloma, as it is practically always within the areolar area or within the terminal ducts of the nipple itself. If blood comes through a duct of the nipple, one can usually localize it by two methods.

First: Stroke gently but with the necessary degree of pressure from the areolar edge up to the nipple itself. It may first be necessary to cleanse the nipple thoroughly with soap and water, in order to dislodge the dried clot which may be imbedded in the very terminal portion of the duct, and which may be responsible for not allowing free flow from a duct that is filled with blood and papilloma. By stroking carefully over the entire area surrounding the nipple, one is usually able to find a place pressure on which produces the bloody discharge on the nipple surface. As a rule, when one locates this, he will find a faint thickening or a definite elongated area representing the widely dilated duct which is affected.

Secondly: In cases where there is a definite bloody discharge, the transillumination light will reveal a black streak leading from the nipple

to the papilloma. This black streak represents the shadow of the blood-filled duct. The picture is very striking when it can be demonstrated.

In cases of sero-sanguineous, lemon-yellow, or clear serum discharge, the light is of little value in localization.

In a study of 129 cases of papilloma, papillary cystadenoma, and papillary cystadenocarcinoma (the malignant stage in the life history of the tumor) I found that the difference in the age group of the patients with the lesion still benign and patients with the lesion malignant, was a spread of twelve years. I therefore drew the conclusion that it took a period of years for a papilloma to become a malignant tumor.

3. *Cysts.* I mention cysts, cystic mastitis and cystic disease of the breast only for the purpose of discarding them as precancerous lesions. There are some, however, who believe these lesions to be precancerous; this group is championed by Shields Warren of Boston. I do not believe these lesions represent precancerous states. If cancer develops in a cystic breast, it is a coincidence and not due to the presence of cysts. Literally thousands of cases of cystic disease occur, which lesions disappear without ever having been seen by a doctor. Cystic disease is an ovarian hormone imbalance disease which is spontaneously terminated with the appearance of the menopause. Above all else the clinician must be certain that he is dealing with a cyst or cystic disease and it may require a biopsy or needle puncture to determine this.

4. In the young woman from 20 to 35 years of age, it is common for premenstrual lumps to appear, then disappear after the period. In this age group, I am not quick to operate, preferring to allow a reasonable time to elapse before suggesting a removal of the lump.

In the succeeding 10 to 15 years, however, I do not hesitate to remove the lump which is a localized area of mastitis. In a study of such cases, we have found that following the years of active menstruation, it is at exactly this site that a carcinoma may develop. During the post-menopausal years, the mammary gland undergoes almost complete atrophy, but the area of mastitis frequently persists and one portion of it may become carcinomatous. It is therefore wise to remove a persistent area of mastitis in women over 35 years of age.

5. In recent years, a lesion of the breast was described by Stewart and Foote which they termed "tubular carcinoma in situ." In its early stages, before any clinical signs are developed and before there is any extension into surrounding lobules, the lesion is easily cured

by a simple local excision of the tumor itself. In fact, the finding of most of these tumors has been accidental during the course of operating on some other growth. This lesion has been considered to be precancerous by some pathologists. However, it may develop into a true carcinoma. It should be locally removed; but as most of my experience with it has been in connection with another lesion, it is difficult to make a pre-operative diagnosis as it lacks clinical signs. Later stages of "carcinoma in situ" show it capable of metastasis and full fruition as a carcinoma.

6. Certain breasts are the seat of a chronic irritation due to stasis. The ducts are widely dilated, and are filled with a putty-like material which remains as a source of infiltration by leukocytes. Ewing has often pointed out that there is a close association of mammary cancer and duct stasis. This correlation of stasis and cancer is denied by Stewart. We frequently obtain in these stasis cases large amounts of thick, dirty material by stroking toward the nipple and emptying, at least temporarily, the large terminal ducts. It is not possible to clear the entire breast by mechanical means; but it is possible that by this manipulation, we may obtain a reduction of the chronic irritation within the breast.

Cervix Uteri: It is generally conceded that carcinoma of the cervix usually develops in the presence of lacerations, erosions, bacterial infections and putrefaction—a combination of mechanical insult and chemical irritation.

The incidence of cancer of the cervix can be materially reduced by the mechanical repair of the lacerations and erosions; and by improvement of environmental conditions, such as by the practice of daily douches.

Smith of the Woman's Free Hospital of Boston, and several other observers have been impressed with the great local improvement in the cervix following electro-desiccation of a badly lacerated and infected cervix. And it is their belief that cancer rarely develops after such an electro-desiccation repair. Pemberton cites 1087 cases in which repair of the cervix was done. Cancer developed in from 5 to 36 years subsequently in only 23 cases (2 per cent).

Fewer opportunities would be present for the development of cancer of the cervix if, instead of performing a supracervical hysterectomy for a fibroid uterus, a complete hysterectomy, including the cervix, were done.

Because of the almost complete absence of cancer of the cervix in Hebrew women, it could be inferred that if circumcision were universally practiced, there would be, in all probability, less infection of the cervix, with a resultant lessening of the disease.

Reduction in the number of cases of cancer of the cervix can be effected not only by changing the environment, as suggested above, but it is especially in this field that one of the newer contributions of great value has been made to American medicine by Papanicolaou. His study of the vaginal smear cells is a contribution which gives those familiar with it a valuable clue in recognizing early carcinoma. Papanicolaou's study is a decided advance in the early diagnosis of cancer of the cervix, making possible the recognition of early lesions within the canal before they come within the realm of clinical observation.

This profitable study has been more selectively carried out by Ayre and his co-workers at McGill University, who state that "the cervical cytology smear will differentiate in over 95 per cent of cases." (Personal communication.) Their study shows "that the cervical aspiration is so accurate that in a survey of over 2,200 cases, the average deviation between cytology and biopsy was only 2.96 per cent." Ayre also describes a series of clinically normal-appearing cervixes where the cytology test diagnosed pre-invasive cancers before there was even any clinical indication to do a biopsy.

These additions by Papanicolaou and by Ayre are scientific contributions of enormous value in the field of the cure of cancer.

In carcinoma of the body of the uterus, much investigative work remains to be done in the field of a hormone approach to the problem. It is generally believed that the development of adenocarcinoma of the corpus uteri is much dependent on the ovarian hormone influence. The environment of the uterine lining could be modified by androgen and estrogen therapy; and it is conceivable that androgen therapy might retard the development of a carcinoma of the body.

Lungs: Among those most familiar with the development of adenoma and carcinoma of the lung, there is growing a feeling that the inhalation of smoke is playing an important role in the great increase of lung tumors. Dr. Ochsner of New Orleans is fond of demonstrating the parallel between the increase of cancer of the lung and the increase in the consumption of cigarettes. The lines are exactly parallel.

The air of our cities is filled with smoke dust, circulating dirt and

burned gasoline fumes. The lungs of the city dweller today are subjected to irritation that their forefathers never experienced.

In certain chemical factories, where there is little opportunity for fresh air to circulate, the workers are subjected to hours of irritation of the bronchi and the bronchiolar lining by acrid gases and suspended dust.

Bladder: In recent years, a perfect experiment was unwittingly conducted in the production of cancer of the bladder. In a nearby city there was a chemical factory whose workers developed a very high incidence of bladder cancer. The management became concerned and had a study made of the local industry. It was shown in the investigation that under the conditions in which the men had to work, they inhaled chemical fumes in large amounts; and these chemicals, which were excreted and recoverable in the urine, were the cause of the bladder cancer. The prophylaxis naturally lay in supplying fresh air to the workmen. Modern ventilation equipment was installed, with the resultant elimination of cases of cancer of the bladder.

Carcinoma of the Testis: For a long time it has been recognized that carcinoma develops much more frequently in cases of undescended testis than when the testis is in the normal position. It is obvious that a good preventive against the development of carcinoma testis is the bringing down into the scrotum of undescended testes, in youth by the injection of testosterone propionate, and in adult life by a surgical operation.

Carcinoma of the Pharynx: In the northern countries, such as Sweden and Finland, where part of the population lives within the Arctic Circle, the principal diet during a large part of the year is reindeer meat and salt fish. Only for a short time are green vegetables available, and as a result, these people develop a condition of the pharynx and tongue known as Plummer-Vinson's disease. It is an avitaminosis, and the disease eventuates in cancer of the pharynx and tongue. By giving these patients sufficient vitamins, Plummer-Vinson's disease can be definitely stopped, so that no cancer will develop.

Stomach: The chronic irritations to which the stomach is subjected are almost too numerous to mention—thermal, chemical, and mechanical.

It is an all too common habit of certain people to drink soup, coffee and other beverages so hot that they must hurry the drink down because their mouths are being burned; and once past the throat, what happens

to the stomach when the scalding liquid hits it is a matter of indifference to them, the stomach having no particular sensation for heat, or excessive heat. The liquid may be entirely too hot to hold the finger in, but the poor stomach has to take it, no matter what the damage to the stomach mucosa.

The great American habit of the drugstore lunch, where stenographers and business men snatch a quick sandwich and wash it down with hasty gulps of hot coffee at the soda fountain, while the next customers stand behind them, breathing down their necks and trampling on their corns, is certainly not conducive to the peace and relaxation which should accompany mastication and the ingestion of food.

The stomach mucosa is a delicate but jealous structure. It must be handled with proper respect because it has the power to throw out on insult sufficient hydrochloric acid to burn a hole in the wall of the stomach. And once an ulcer develops, it is difficult to heal and becomes the source of a possible carcinoma. I am not overlooking the old controversy of which came first, the ulcer or the carcinoma. But we do know that repeated healings of any ulcer, as, for example, a burn scar, brings with it the possibility of the development of a carcinoma.

It has often been noted that those with marked pyorrhea seem to be better candidates for the development of a gastric carcinoma than individuals with uninfected mouths.

The American appetite for alcohol in almost any guise remains undiminished in spite of the fact that it can easily be demonstrated microscopically that a cocktail, for example, acts as an insult to the gastric mucosa, producing a temporary gastritis. Fortunately for the tipplers, the mucosa is restored within a period of a few hours. The work of Ivy of Chicago on gastritis is extremely impressive, as it shows how very delicate the gastric mucosa actually is and how quickly it repairs itself.

I am inclined to feel that eating a large meal at a time when one is physically exhausted is a bad habit, as the muscular action of the organ is much delayed, and the food lies in the stomach as an irritant for several additional hours.

Mouth, Tongue, Cheek, Tonsil: I have saved for the last a discussion of the classic example known to every medical graduate. Cancer of the mouth, tongue, tonsil, and inside of the cheek is found to a large extent in cases demonstrating pyorrhea, sharp teeth, ill-fitting dentures, smoking in excess, or syphilis.

Of all the types of cancer, the intra-oral group is the most easily prevented. A sharp or broken tooth can be ground down. A tooth standing out of alignment can be, even if it is only moderately sharp, the source of a constant mechanical injury to the tongue—which is an organ never in repose except during sleep. The cheek or tongue constantly rubbing against a denture that is sharp or rough can be mechanically torn many times a day. These mechanical insults in the presence of chronic infection of the mouth due to lack of dental hygiene, frequently are the cause of intra-oral cancer. Excess smoking constantly produces a burning of the tongue and cheeks and lip. Intra-oral cancer develops notoriously in the presence of syphilis and leukoplakia. The prevention of mouth cancer therefore lies in the correction of pyorrhea and of ill-fitting dentures, of repairing broken and sharp teeth, of changing the smoking habits, and of curing lues.

Conclusion: I have discussed nearly forty ways of interfering with the development of specific cancers. We have the means at hand. If the public and the medical profession were to give more serious attention to our present possibilities of *preventing* cancer, the magnitude of our cancer problem would be materially lessened.

THE EARLY DIAGNOSIS OF CANCER *

ELISE S. L'ESPERANCE

Director of Kate Depew Strang Cancer Prevention Clinics,
Memorial Hospital and The New York Infirmary

It is a privilege to be invited to contribute to this program the information obtained from our cautious experiment in cancer prevention and early diagnosis.

Cancer is one of the major problems in medicine today and early diagnosis is the corner stone on which the entire structure of cancer control rests. Therefore, the early diagnosis of cancer or if possible its prevention should be a constant responsibility in the mind of every practicing physician.

During the past, the greatest emphasis has been placed on research and the progressive development in the various methods of treatment. Irradiation therapy was received with great enthusiasm, first as the sole method of treatment and later combined efficiently with surgery. Miracles have been performed through the union of these two effective members of the physicians' armament against cancer.

The curative benefits of these *should not be minimized*, for records show an ever increasing number of cases alive after five, ten or even fifteen years following this scientific treatment. Still, cancer continues to occupy second place in all recorded deaths in the United States. We may partly explain this discouraging prospect by balancing it against the fact that life expectancy has increased by fifteen years in the last half century, and with the advances in accurate diagnosis, a greater number of cancers would be recognized. Even this rather questionable explanation does not entirely serve to account for the continued increase.

Progress in treatment does not always control or eradicate a disease or materially reduce the mortality, no matter how efficient and praiseworthy. Take typhoid fever for example, although we know the cause, the ultimate control of this disease depends largely on preventive medicine. And this applies to many other serious diseases.

* Presented October 18, 1946, before the 19th Graduate Fortnight of The New York Academy of Medicine.

In 1926 Ewing stated that "in the control of cancer, prevention must play a prominent role for it appears more and more evident that early diagnosis alone is not capable of accomplishing the desired reduction in death rate."

Yet prevention and early diagnosis in cancer have been neglected these many years. Possibly this is due to the fact that the cause of cancer is unknown, and it is the generally accepted theory that the cause of a disease must be known before it can be adequately controlled. Even though we do not know the etiology of cancer, nevertheless we have very definite knowledge concerning its life history. We know that cancer does not develop suddenly in previously normal structures, but slowly, often following prolonged irritation, and requires a certain time interval to become fully malignant. It is in this quiescent period between the local disease and the full blown cancer that early diagnosis can play such an active part. *For effective treatment is that instituted at a time when the process is localized.*

The problem of early diagnosis in cancer is by no means an easy one, for in its earliest phases there may be few characteristic symptoms usually not of sufficient diagnostic importance to be recognized except by well trained physicians. Furthermore, the protean nature of cancer which is apt to masquerade under the guise of a host of common disorders, and may involve any organ in the body from birth to old age, presents a situation which requires considerable fundamental training and the keenest clinical judgment. Perhaps it may be insufficient training, undue optimism, or overwork among practicing physicians which accounts in part for the high incidence of advanced undiagnosed cancer that reach the specialist in an incurable stage. But an important element in the failure to obtain an early diagnosis is the difficulty encountered in persuading patients to seek medical aid promptly. The dominant reason for this hesitation on the part of the public to consult physicians is the fear that they might discover they had cancer. The active propaganda campaigns of the American Cancer Society have done much to overcome this latent dread of the disease and they have created an eager interested people willing to avail themselves of any opportunity which might prevent their falling a victim of cancer. This placed the responsibility of providing the facilities for the possible prevention and early diagnosis of cancer squarely on the shoulders of the physician. There appeared to be only one way that this obligation could be met,

TABLE I
STRANG CANCER PREVENTION CLINIC—NEW YORK INFIRMARY

	1944	1945
Total Patients	370	1047
Age Groups		
Under 40	283	530
Over 40	187	517
Family History	157	478
No Family History	213	569
Cancer	7 (2%)	11 (1%)

TABLE II
STRANG CANCER PREVENTION CLINIC MEMORIAL HOSPITAL

<i>Diagnoses</i>	1940	1941	1942	1943	1944	1945
Cancer	4	7	38	21	17	31
Benign Tumors	4	35	130	136	206	523

TABLE III
STRANG MEMORIAL PREVENTION CLINIC—MEMORIAL HOSPITAL
GROWTH OF CLINIC

	1940	1941	1942	1943	1944	1945
New Patients	16	150	519	507	1039	3066
Return Patients	9	161	592	1077	1653	3161
Total	25	311	1111	1584	2692	6227

that was by *periodic cancer health examinations* of presumably well individuals. The public was interested and anxious to coöperate and it seemed that some way should be found to provide the opportunity for such examinations. Therefore, in May 1937 as a cautious experiment we designated a special clinic day in the Kate Depew Strang Tumor Diagnostic Clinic of the New York Infirmary for the complete physical examination of apparently healthy women who were anxious to know

TABLE IV

STRANG CANCER PREVENTION CLINIC—MEMORIAL HOSPITAL
ANALYSIS OF MAJOR DIAGNOSES IN 1945

Total New Patients Seen	3066
Cancer	31
Benign Tumors	523
Fibromyoma	74
Nevi	67
Lipoma	24
Thyroid Adenoma	9
Papilloma (Skin)	24
Other Conditions	1958
Hypertensive Cardio-Vascular Disease	71
Chronic Cervicitis	316
Mastitis	184
Tuberculosis	5
Diabetes	2
No Evidence of Disease	174

if they had cancer. This was the first organized attempt toward possible prevention and early diagnosis in cancer. *It was a tentative plan to prove whether prevention and early diagnosis in cancer could become a practical part of a medical health service.*

There was considerable discussion and debate as to the justification of the use of the term "Cancer Prevention Clinic." If the public could be persuaded to bring their early cancers to the physician for diagnosis, how much more readily would they come for examination if there were the slightest hope that the development of cancer may be prevented. This is sound psychology and the phenomenal growth of the Strang Cancer Prevention Clinics substantiates such a theory.

In 1940 a similar Cancer Prevention Clinic for women was opened at Memorial Hospital, and in 1944 such a Clinic for the examination of men was established there. In the first year at the New York Infirmary, seventy-one women were examined, and in 1945, five thousand three hundred and twenty five new patients, which included men and women, were examined in all the Cancer Prevention Clinics at both institutions.

One may well ask what is meant by the term "Prevention and

TABLE V

STRANG CANCER PREVENTION CLINIC—MEMORIAL HOSPITAL

Source of Patients	1941	1942	1943	1944	1945
N.Y. C.C.C.	60	221	177	140	99
Publicity	27	157	112	574	1898
Memorial Hospital	32	58	66	62	42
Strang Patients	16	54	109	209	976
Local M.D.	15	18	23	36	51

Early Diagnosis of Cancer." Really they are different steps in the same process and have the same ultimate goal: that is, the prevention of fully developed malignant tumors through early diagnosis. In our Clinics we consider all the predisposing factors that may precede or predispose to cancer and of these there is a vast amount of knowledge.

It is well known that many forms of chronic irritation, long continued, produce an inflammatory hyperplasia, often designated as precancerous, which if the irritant continues may and frequently does become transferred into cancer; in a comprehensive physical examination all of the possibilities must be taken into consideration. For example, the chronic irritation produced by ill-fitting dental plates, excessive use of tobacco and syphilitic leukoplakia may tend to induce a wide variety of cancers of the mouth, lip, and tongue, as well as the larynx. Eliminate these factors and the incidence of intraoral cancer should largely disappear. Persistent hoarseness or intermittent loss of voice should make the keen observer suspect carcinoma of the larynx and a laryngoscopic examination is the best means of early diagnosis, supplemented by a surgical biopsy of suspected lesions. Likewise, in early carcinoma of the tongue, leukoplakia which begins to crack open or a deviation on protrusion may be the earliest sign that cancer is imminent.

In cancer of the skin we have a wide variety of precancerous dermatoses, and the larger group of papillomata. The small persistent white nodules which mark the beginnings of basal cell carcinoma may be recognized and treated early before they become active. Then there are the pigmented and nonpigmented nevi, many of which are potential melanomas, and if in an area subject to irritation should receive the most expert attention.

The small basal cell epidermoid carcinoma usually occurring on the face, if recognized early, may be completely cured by radiation.

Mammary cancer still appears almost beyond the reach of effective prevention and early diagnosis. The very subtleness of early cancer in a functioning organ such as the breast adds a disturbing factor to the interpretation of diseases there. Simple palpation of the breast is too often neglected in a physical examination. Nevertheless such an examination when done by a well trained physician may give invaluable information and with a little experience one may differentiate by this means, chronic mastitis, simple cysts and fibroadenoma from early carcinoma. There is quite a distinct difference in the distribution, consistency and the degree of fixation to the surrounding tissues in these various lesions. The best preliminary training for the early diagnosis of breast cancer is to form the habit of examining all normal breasts at different ages.

We rely almost exclusively on the periodic manual examination of the breasts in all cases as the most satisfactory guide for further diagnostic investigation of any disease in the breast. In the presence of any suspicious lesions all the special aids in diagnosis of cancer of the breast are brought into action until an accurate diagnosis is reached.

Transillumination of the breast is of value in differentiating cystic from solid tumors, large duct papillomas, sarcomas, and hematomas, but is inferior in accuracy to the aspiration biopsy.

Soft tissue x-ray of the breast as described by Warren,¹ while difficult of interpretation, still in the hands of an experienced radiologist may give suggestive information. It is especially useful in large heavy breasts where palpation is difficult. Scharnagel² examined seventy cases of tumors of the breast by this method and the results indicate that it may be of assistance in differentiating benign from malignant tumors.

The aspiration biopsy (H. E. Martin³) when properly employed gives very dependable information and is of unquestionable value in recognizing early carcinoma of the breast. As carried out in our Clinics at Memorial Hospital and the New York Infirmary it affords a fairly rapid and accurate method of determining the nature of neoplasms of the breast. In a series of 100 cases of breast cancer from the Tumor Diagnostic Clinic at the New York Infirmary, 64 per cent were positive by aspiration biopsy; 28 per cent showed suspicious cancer cells, thus giving a high degree of accuracy by this simple means. All

of these cases were confirmed by surgical biopsy or the clinical course of the disease. The hazards of this method seem negligible, for Stewart reports no harmful effects following this procedure.

A negative report, however, is of no significance, and in the presence of clinical evidence of disease, the removal of the breast nodule with provision for immediate gross and microscopic examination of tissue is indicated.

The most frequent cancer in women is that involving the uterus and it is responsible for about 30 to 35 per cent of deaths from this disease.

In 1938 Catharine Macfarlane⁴ of Philadelphia established a specialized clinic for the examination of 1000 apparently normal women to determine the value of periodic gynecological examinations in the prevention and early diagnosis of cancer of the uterus. She found 1.8 per cent cancer among these women. Her results indicate the importance of treatment for the host of chronic inflammatory diseases encountered in the cervix, many of which have potentialities of future carcinoma.

In the recognition of early carcinoma of the cervix we employ every diagnostic aid.

The Schiller Iodine Test gives some information but little more than can be obtained by an accurate survey.

The Papanicolaou⁵ vaginal smears and the direct cervical smear occupy an important place and are routine on all our cases. In the presence of a suspicious lesion a surgical biopsy is the method of choice.

The role of surgical biopsies in the early diagnosis of cervix cancer can hardly be overemphasized. Evidence to support this is based on the results obtained in our Clinics. During the past year at Memorial Hospital, Stewart and Foote have confirmed nine of our cases of intraepithelial epidermoid carcinoma—carcinoma in situ—by this means, when a simple amputation of the cervix may be effective. It suggests the advisability of establishing this rather simple measure as a routine. We are not satisfied with one negative report if there is a lesion of the cervix. This is well illustrated by a recent case. This young woman had a positive cervical smear but the report of the surgical biopsy was negative. The biopsy was repeated and the lesion proved to be early carcinoma.

The future value of this method is further strengthened by the recent report of Pund and Auerbach⁶ who examined, in serial sections,

TABLE VI

SUMMARY OF CLINICAL APPLICATION OF VAGINAL SMEARS AS A ROUTINE PROCEDURE—JANUARY 1, 1945 TO JANUARY 1, 1946 AT STRANG CLINIC, MEMORIAL HOSPITAL AND NEW YORK INFIRMARY

Total Number Cases Examined (Cervical and Vaginal Smears)	7168
Positive Diagnoses Made From Smears	67
Positive Diagnoses Confirmed by Biopsy	26
Positive Diagnoses Refuted by Biopsy	17
Cases Which Were Not Followed by Biopsy	24

1200 surgically removed cervixes and state that preinvasive carcinoma was discovered in 47 or 3.9 per cent of the cases so examined. No gross manifestations of carcinoma were found in any of them. The average age of the patients was 36.6 years as contrasted with 48 years, the usual age of fully developed cancer of the cervix. This seems to substantiate the theory long held by Ewing and Fred Stewart that the latent period of quiescent cancer may be from five to ten years or more; and that the carcinomatous process is a distinctly evolutionary one having a local starting point and pursuing a known course to a definite termination. Therefore it is reasonable to infer one may encounter the disease in any one of its phases.

Prevention and early diagnosis in cancer of the fundus is more difficult and dependence should be placed on the routine vaginal examination as the most effective measure associated with the endometrial aspiration biopsy. Uterine bleeding is always suspicious, but unfortunately is not an early symptom of carcinoma of the fundus. When it does occur it may be due to atrophic endometritis, an endocrine disturbance, or even hypertension. Only a careful analysis can decide the nature of the disease. All diagnostic adjuncts including a uterine curettage should be employed before reaching a final conclusion.

Smears by the Papanicolaou method are useful in determining the necessary future steps to arrive at a diagnosis. In our experience if repeated positive smears are obtained and no evidence of disease of the cervix is observed on vaginal examination it is an indication for a uterine curettage to determine the presence or absence of carcinoma of the fundus.

The significance of these positive smears is not always evident to

TABLE VII

STRANG CANCER PREVENTION CLINIC—MEMORIAL HOSPITAL

Disposition of Patients	1942	1943	1944	1945
Local M.D.	150	103	239	759
Memorial Clinics	62	59	51	123
Other Clinics	46	39	32	38
Observation	250	287	717	2146

the general practitioner and as we refer our cases to the physician for treatment, it not infrequently happens that there is an unfortunate delay in obtaining the diagnostic curettage.

The importance of this is illustrated by a case in our Clinic at Memorial Hospital. A patient with three positive vaginal smears was referred to her physician with the report of our findings and the information that in our experience this indicated the necessity of a uterine curettage to determine the condition of the endometrium. Three months later the patient revisited our Clinic and reported that her physician did not deem the operation necessary. On examination these smears were again positive and her physician was so notified. Six months later she returned with uterine bleeding and a fully developed adenocarcinoma of the fundus.

In gastro-intestinal carcinoma the only form of early diagnosis available is the use of all means at our disposal for the recognition of the earliest evidence of gastro-intestinal lesions. A routine gastro-intestinal radiographic examination is the most satisfactory method at the present time. Whether one is justified in submitting all normal persons to this examination must be decided in the future. We have not attempted such a procedure in our Clinics but have limited our gastro-intestinal x-ray examinations to patients with vague gastric or abdominal symptoms. This method has paid dividends many times in the early diagnosis of unsuspected duodenal and peptic ulcer, in one case of gastritis polyposa and two cases of gastric carcinoma. Recently we have instituted a fluoroscopic investigation of the stomach in presumably healthy persons over 45 years of age in coöperation with the Radiographic Department of Memorial Hospital. So far this has yielded rather interesting facts. In the first 505 cases examined an extremely unusual myosarcoma

of the lower esophagus in a young woman without symptoms was recognized at a stage which permitted successful operative procedure. Whether such examinations will prove of sufficient practical importance to be included as a routine in cancer health examinations will depend on the results obtained in a long series of cases interpreted by an experienced radiologist. A gastro-intestinal x-ray series, gastric analysis, esophagoscopy and gastroscopic examinations should supplement the gastric survey in all suspected lesions.

Prevention and early diagnosis in rectal cancer depends largely on the skillfulness of a thorough rectal examination of all cases. In the Cancer Prevention Clinic at Memorial Hospital a proctoscopic examination under the direction of the Rectal Department, of persons over 45 years of age has been added as a routine practice for the past six months. In 194 cases without symptoms, examined in the Men's Department of our Clinic, two cases of silent carcinoma of the rectum were discovered. In the entire group of 299 cases with and without symptoms examined with the proctoscope four cases of rectal and sigmoid carcinoma were added to the general statistics. The incidence of rectal polyps in these 299 cases becomes of interest as they are considered precancerous lesions. We found 14 in the rectum and 4 in the sigmoid. In the women's service two cases of symptomless cancers of the rectum were also found by this investigation.

Bladder carcinoma may usually be traced to some form of chronic irritation, such as stones and chronic cystitis. In Egypt this is well illustrated by the fact that ten times as many individuals infected with *Schistosoma haematobium* develop cancer in contrast to those unaffected. Examination of urine sediment smears as carried out by Papanicolaou and Marshall⁷ may be of value. However, all cases of cystitis and urinary calculi should receive prompt and thorough cystoscopic examination with a pyelogram.

The relative frequency and insidious nature of carcinoma of the lung warrants a routine radiographic examination of the chest in all cases. In the presence of any definite pathology recourse should be had to the bronchoscope or the Craver needle for aspiration biopsy. This enables the physician to obtain a fairly accurate pathological report in the shortest possible time.

The most important single method at our disposal for the early diagnosis of cancer is the *comprehensive periodic physical examination*

of *an individual* by a physician on the alert to recognize early signs of cancer. This is illustrated in a patient who came to our Prevention Clinic complaining of a lump in the breast which proved to be a simple cyst, but the complete examination revealed early unsuspected carcinoma of the cervix.

The physical examination as performed in the Strang Clinics is not limited to any part of the body, but includes a complete survey of the skin surfaces, nasal and oral cavities, eyes, ears, blood pressure, height and weight. The chest is examined by percussion, auscultation and Roentgen films. Palpation of the abdomen is followed by a pelvic examination which includes a vaginal and cervical Papanicolaou smear on all cases, with surgical biopsy on suspicious lesions. A manual rectal examination is routine with proctoscopic examination of all cases over forty-five years. A complete blood count, a urinalysis and a serological test for lues are performed. This entire procedure is repeated at the annual re-examination of the patient.

In our experience the routine blood count has been the means of identifying two cases of early leukemia. Also in a case of presumed arthritis we found Bence-Jones protein in the urine and later confirmed our suspicions of myeloma by radiographic examination of the bones. In another case a positive Kline test gave us the lead for a difficult tongue condition which suggested early carcinoma.

One of the most dependable aids in the early diagnosis of cancer is the aspiration biopsy. This simple technique if properly employed may be applied to both accessible and inaccessible neoplasms. Its use is not limited to any one organ but the accuracy of the diagnosis depends on the skill of the operator and the knowledge of the pathologist. In one of our cases a diagnosis of primary carcinoma of the liver was made on the aspiration biopsy which was later confirmed at an exploratory laparotomy.

Accessible lesions usually give rather definite evidence of their nature by this method. However, a negative finding should be regarded as of little value in the presence of suggestive clinical symptoms. The risk of spreading cancer by aspiration biopsy has been proven negligible (Stewart).

The surgical biopsy is still the most dependable and accurate means of diagnosis in early cancer. It gives an indisputable record readily obtained and has a wide range of usefulness. In the cervix with the use

TABLE VIII

STRANG CANCER PREVENTION CLINIC—MEMORIAL HOSPITAL
ANALYSIS OF CANCERS

		Age				Symptoms		Site of Primary			Total	
		21—30	31—40	41—50	51—60	60+	With	Without	Skin	Breast	Cervix	Misc.
1944	0	5	4	5	3	13	4	4	6	2	5	17
1945	0	7	8	10	6	21	10	15	3	4	9	31

of a biopsy forceps it is a simple painless procedure and should be employed in all suspicious lesions in this region. It is also of value in determining the nature of rectal pathology and with the aid of the proctoscope it is a relatively minor undertaking.

In skin lesions it may be a little more difficult, requiring local anesthesia. It is the only way, however, to arrive at an accurate conclusion as to the nature of the disease. Where the skin lesion is of small size removal of the entire tumor mass is preferable. This applies especially to the innocent looking pigmented nevi which should be removed with a rather wide margin.

Vaginal smears by the direct or Papanicolaou method deserve a prominent place in all gynecological examinations. They are of especial significance for the reason that they may indicate the presence of early carcinoma before other gross signs or clinical symptoms are present.

Jones in a Research Project⁸ in the Strang Department has examined 8,636 cases by the smear method from varying types of gynecological disease including suspected or unsuspected cancer with the following results. Of these approximately 8,000 cases, 311 were positive and 81 of these were confirmed by biopsy. Nineteen were not suspected clinically, 152 were not verified by biopsy and seventy were refuted by the biopsy. Even with a possible source of error of interpretation we consider this test as an essential part of a pelvic examination and of sufficient practical importance to justify a thorough investigation of any case in which such a test is positive. There are several advantages in this technique in early diagnosis of cancer: First, its extreme simplicity of operation and second, the fact that the cell changes encountered often precede any gross manifestation of disease.

The positive diagnosis of cancer, however, must rest on the histological report of a surgical biopsy or a uterine curettage. For the serious

implications both to patient and physician embodied in the final diagnosis of malignant disease places a tremendous responsibility on the pathologist. Therefore his interpretation should be supported by every dependable diagnostic means.

We had a rather interesting experience with the Papanicolaou smears. A young woman with vaginal bleeding from whom two positive smears were obtained was recommended to have a uterine curettage. The curettings, however, were negative for cancer. Later as the symptoms continued a laparotomy was performed on the probable diagnosis of ovarian cyst, and a bilateral carcinoma of the fallopian tubes was found.

The possibilities of the smear method of diagnosis are limitless. They may be applied with considerable assurance to almost any secretion of the body. Papanicolaou and Marshall⁷ have reported interesting results from examination of urinary sediment for suspected carcinoma of the genito-urinary tract. Similar methods have been applied to sputum in suspected cancer of the lung and in gastric washings for cancer of the stomach. All of these are still in the investigation period and few statistics are available. With further research this method may become of considerable value as an aid in early diagnosis.

In the recognition of all internal and inaccessible cancers, radiographic examination is indispensable. X-ray of the chest in all persons over 35 years of age should be a routine procedure. We include two cases of carcinoma of the lung brought to light by this means.

The differential value of a radiographic examination in all tumors of bone should indicate its wider use in the health examination of young persons. All of these procedures may be carried out in the clinic with ease and safety.

This detailed description of diagnostic methods employed in the Strang Cancer Prevention Clinics⁹ is given to emphasize the necessity of a thorough examination which utilizes all the newer diagnostic techniques available to arrive at an accurate diagnosis. Anything short of this may confer a false sense of security to the patient. Each test has been added with the definite purpose of increasing the efficiency in early diagnosis and is often undertaken to evaluate various highly specialized examinations in the diagnosis of obscure or inaccessible cancers.

It is our purpose to continue to maintain this definite research point of view in regard to expansion in both our Strang Cancer Prevention Clinics. We feel that by our association with the Memorial Hospital

TABLE IX

STRANG CANCER PREVENTION CLINIC—MEMORIAL HOSPITAL
MEN'S CLINIC—ANALYSIS OF DIAGNOSES
NOVEMBER 1944 TO JUNE 1946

Total Patients			1329
Cancer			13
Precancerous Lesions			79
Benign Tumors			282
Prostatic Hypertrophy			59
Hemorrhoids			119
Hernias			68
Hypertensive Cardio-Vascular Disease			101
Peptic Ulcer			65
Proctoscopic Examination			
Survey	194	} Cancer	5
Diagnostic	105		18
Total	299		

Cancer Center we have the opportunity to determine their diagnostic value for the information of future cancer prevention.

These Clinics are maintained for the early diagnosis and possible prevention of cancer only. No treatments are given. One of the important objectives is to encourage the habit of periodic consultation with a physician or clinic, annually for persons under 40 years of age and every six months for those over 40 years, as the best means for the early diagnosis of cancer and to maintain the general health of a community.

What have we learned in the past nine years from this cautious experiment in the early diagnosis and possible prevention of cancer? The Clinic at the New York Infirmary began with seventy one patients the first year. That was in 1937, and in 1945, 1027 new patients were examined and 800 returned for re-examination.

At the Memorial Hospital Women's Clinic 184 women patients were examined during the first thirteen months after its organization in November 1940. In 1945, 3066 new patients were examined and 3161 return visits were made, that is to say a total of 6227 patients in one year. Approximately 40 per cent of all these persons came to the clinics in both hospitals without symptoms or noticeable evidence of

disease. Of these, *one and one-half to two per cent*, varying from year to year were found to have early cancer. About 20 per cent had benign tumors; 9 per cent had precancerous lesions; 43 per cent revealed some unsuspected constitutional disease, and only 16 per cent were found to have no evidence of disease. Sixty per cent revisited the Clinic within one year and 10 per cent within six months.

In the Men's Clinic at Memorial Hospital during the 20 months since its organization, 1329 patients were examined. Of these 13 had cancer; 18 had precancerous rectal or sigmoid polyps, and 48 had some form of leukoplakia of the oral cavity.

In conclusion one may be permitted to mention a few important points gleaned from these Clinics as future possibilities in the successful prevention and early diagnosis in cancer.

The accumulated data contained in the histories of these individuals over a period of years will furnish a basis for the scientific clinical research of many factors involved in the cancer problem, such as the relationship of heredity, mode of life, age incidence, precancerous lesions and diseases to the development of cancer.

The diagnostic results obtained offer convincing evidence of the importance of periodic cancer health examinations in the control of cancer and possibly a host of other diseases. The rapid growth demonstrates the willingness and desire of the people to accept such a program. This demand by the average person gives an opportunity to the medical profession to utilize this enthusiastic response and develop universal periodic cancer health examinations of presumably well persons.

The Medical Society of the County of New York has recently endorsed the proposal of the New York City Cancer Committee to sponsor and establish Cancer Prevention Clinics in a group of voluntary hospitals in New York City. It is to be hoped that every large community will follow this example.

The Department of Preventive Medicine in Cornell University Medical College has recognized their value in the teaching of cancer and for the past year groups of students have attended sessions of our Clinics at Memorial Hospital as an integral part of their clinical training. The expansion of such a program of undergraduate teaching is now receiving serious consideration and may be the first step in the realization of a significant advance in cancer education. One of the

weakest links in the program of prevention and early diagnosis in cancer is the lack of adequate training of medical students in this subject.

The organization of a special department of neoplastic diseases in medical schools to correlate the various aspects of cancer would do much to obviate this deficiency and prepare the future general practitioner for some of the hazards of cancer diagnosis.

Every year witnesses some advancement toward the solution of the cancer problem. Yet viewed in the light of our present knowledge there seems much still to be accomplished. The future possibilities of cancer prevention are still undeveloped. We have a waiting list of approximately 6000 in this area alone who wish to be examined, and I know this same condition exists in the Chicago, Philadelphia, Pittsburgh and other Clinics. The demand by the public for such service seems very great yet the response on the part of physicians falls far short of the goal.

Specialized cancer education for the medical profession is in its infancy and wholly inadequate efficiently to equip the general practitioner to cope with early diagnosis in cancer. Until treatment, research, education and prevention in cancer have been brought to their full development and work in close coöperation with each other, there will not be any definite decrease in the mortality from this disease.

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TUMORS OF THE EYE AND ORBIT*

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UNCONTROLLED growths of cells without biologic purpose involving the eye are, in the main, not unlike those found elsewhere in the body. In the beginning they have a special local importance and the undifferentiated types have a general significance as well. The relative frequency of benign and malignant tumors in the eye may be explained by the presence of many mixed, interrelated tissues, each dependent on the other, which compose this highly specialized organ. Since the eye lends itself well to examination, tumors are usually observed in their very early stages. But because anatomical or inflammatory changes frequently resemble growths they are not always distinguished and treated promptly and properly.

The tumors which may arise in the eye and its adnexa, and in the orbit are innumerable and discussion of them is quite beyond the time allotted for this presentation. I shall devote the period to recent contributions to the subject and to controversial issues. My material will be presented simultaneously with the showing of illustrations of a number of tumors which were drawn from cases seen at the Eye Institute and with slides indicating the value of the x-ray in the study of expanding lesions of the orbit.

Congenital *naevi* of the bulbar conjunctiva are open to discussion on two points: first, their frequency as the origin of malignant growth and secondly, their relation to benign melanomas of the interior of the eye. The naevus is of neural origin, derived from the end apparatus of the sensory nerve, is usually pigmented and may not be apparent at birth. It is essentially a benign neoplasm which grows very slowly, passes through a long period of quiescence and may eventually atrophy. According to most authors a sudden stimulus to rapid growth may occur, in which event the tumor acquires a capacity to become highly

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malignant. The distinguishing cell of the mole is the large naevus cell which is round or polygonal in shape. These cells may present a gland-like appearance and are found beneath down-dipping prolongations of the surface epithelium. The melanin found in the growth is mainly intracellular, more abundant near the surface and in the central-lying epithelium. Cysts are very frequently present.

The nature and ontogeny of the naevus cells have given rise to much controversy. Masson's¹ recent exposition of the subject that these cells are neither epithelial nor mesoblastic in character but neuro-ectodermal and associated with the terminal neural apparatus is now generally accepted. They are seen associated with the medulated and non-medulated nerve fibres, ending in the skin in Meissner's corpuscles. Some of these cells, less closely associated with the nerves produce pigment (melanoblasts). Wherever a discussion of the naevus is found, one encounters reports of malignant melanoma arising in the naevus. Reese² wrote in 1943 that he had never encountered this circumstance in the eye and in a study of those cases reported in the literature, only two cases could be found which could be identified definitely as cases of melanoma which arose from a pre-existing naevus. He believes that precancerous melanosis may have been mistaken for the mole or that the melanoma was acquired and malignant from the beginning.

The melanomata seen in the iris or choroid are also regarded as naevi but since true naevus cells are not found in these lesions, doubt exists that they are the same. The spindle cells without the processes characteristic of choroidal chromatophores have been regarded as atypical naevus cells. The many references to malignancy arising in naevi in the literature apply to the pigmented spots of the iris or choroid. Reese³ has called attention to the frequency of pigmented spots or freckles in the iris in cases of malignant melanoma. Many others have written of the coexistence of benign melanomata of the choroid with a uveal sarcoma. This has occurred sufficiently often to justify the periodical examination of eyes with benign melanomata. Duke-Elder⁴ has stressed that the occurrence of glaucoma in an eye with a naevus should always be looked upon with the greatest suspicion. By naevus here he is again speaking of a melanoma. Incomplete excision of a melanoma may lead to rapid and uncontrollable growth, as was the circumstance in the case reported by Greenwood.⁵

Reese² has described acquired *precancerous melanosis* as a diffuse,

non-elevated pigmentation with a granular and oftentimes dull appearance of the conjunctiva, appearing usually during the fifth decade of life and showing malignant change in 5 to 10 years. Occasionally the melanosis is malignant from the beginning. It may become so diffuse as to involve almost all the bulbar and palpebral conjunctiva and adjacent skin without causing any localized tumor mass.

Acquired precancerous melanosis has distinguishing histologic characteristics in the benign and in the malignant phase, is radio-sensitive in the precancerous stage and radio-resistant in the malignant. Patients observed by Reese in the malignant stage died. Early exenteration is the treatment advised. Precancerous melanosis should not be confused with 1) congenital melanosis of conjunctiva, 2) melanosis oculi and 3) naevi.

From the several papers which have appeared in the literature in recent years on the prognosis in *malignant melanoma* of the uvea, one gains the impression that this tumor is not as malignant as it was formerly thought to be. Certainly it is not to be compared in malignancy with those arising elsewhere in the body. In their study of 500 malignant melanomas of the eye followed over a period of five years or longer, Callender, Wilder and Ash⁶ of the Army Medical Museum found a mortality of 48 per cent. In 200 cases followed ten years or more, the percentage of deaths rose to sixty-six. They found the average duration of life following operation to be forty-six months. These authors have made a significant contribution to pathology in their study of the malignancy of the various types of malignant melanomas according to cellular structure, reticulin and pigment content.

The single spindle cell variety shows a relatively low degree of malignancy and a heavy fibre content is also evidence of a low degree of malignancy. An increased degree of malignancy is associated with the epithelioid type of malignant melanoma. It was suggested that an increase of malignancy is associated with increased pigment content. Thus, on the basis of microscopic appearance, an opinion can be expressed by the pathologist on the degree of malignancy indicated by the composition of the tumor.

A notable contribution to the treatment of *retinoblastoma* by radiation has been made by Martin and Reese.⁷ In 11 of 24 cases of bilateral retinoblastoma managed by them vision was preserved to some degree by their technique. These authors enucleated the eye with the

more advanced tumor and treated the remaining eye by fractionated doses of roentgen ray totalling 8000 r to each of two portals; $2\frac{1}{2}$ cm. cones were employed and aligned in such a manner as to exclude the anterior segment of the eye from the field. After the tumor atrophied under the treatment the contained calcium became increasingly apparent and finally could be seen as a small bag of concretions. The surrounding retina formerly occupied by the tumor appeared as an atrophic area with proliferation of pigment. This treatment is applicable in those cases in which the tumor is localized to relatively small areas of the retina.

That the calcium content of retinoblastoma may be utilized in the differential diagnosis of the tumor was advanced by Pfeiffer⁸ who found calcium granules in 80 per cent of all of the tumors studied histologically and roentgenographically. Shadows of calcium have never been demonstrated in conditions resembling retinoblastoma.

Aside from epitheliomas of the eyelids which are superficial and easily recognized, *tumors of the orbit* usually displace the eye, or in other words, produce exophthalmos. The diagnosis of tumor of the orbit then involves a study of exophthalmos which may be due to a number of conditions other than hyperthyroidism and tumor. Exophthalmos produced by tumor is usually unilateral but here again the unilateral displacement of the eye is as frequently produced by other conditions. In a series of 200 consecutive cases of exophthalmos studied by roentgenography⁹ the displacement of the eye was caused by benign and malignant tumors and cysts in seventy-two or 36 per cent of all cases. In only 10 per cent of all the cases was exophthalmos produced by a malignant tumor. There were thirteen primary intraorbital neoplasms, eight sarcomas and five mixed tumors of the lacrimal gland in the series. The orbit was involved secondarily in eight cases in which five derived from malignant neoplasm arising in the nasal fossa or sinuses, two from basal cell epitheliomas and one from a myeloma. In the diagnosis of orbital tumor, therefore, a vast number of other conditions have to be excluded. This can best be done by roentgenographic study. In this series of 200 cases there were positive roentgenographic findings in nearly 70 per cent and in 42 per cent of all the cases the findings were diagnostic. Six conditions, that is, retention cyst of a paranasal sinus, meningioma, craniostenosis, neurofibromatosis, deformity of the orbit, and glioma of the optic nerve made up one-third of all

the cases and invariably produced changes which are indicative in the x-ray film.

One of the most confusing conditions in the diagnosis of lesions of the orbit which, in addition, is one of the most common single causes of exophthalmos, is chronic granuloma or so-called *pseudo-tumor* of the orbit. The cause of this inflammatory involvement, which is more frequently unilateral than bilateral and which tends to run a self-limited course, is not known. Lymphoblastoma has been associated in a number of cases. Fortunately, chronic granuloma can be differentiated in most cases by the history and clinical findings and absence of x-ray changes. The onset of this condition is rather sudden, the eyelids are edematous, the exophthalmos is frequently severe, a palpebral mass may be encountered and, in many cases, there is interference with ocular motility. Reese¹⁰ analyzed 30 cases of the literature and found that in 50 per cent of them the patient had been subjected to exenteration of the orbit for supposed malignant neoplasm. Lewis¹¹ stressed the difficulty of getting correct diagnoses from many general pathologists who, he found, are more likely to report that the biopsy tissue represents a true neoplasm.

The paper by McGavic¹² on "*lymphomatoid diseases involving the eye*" deserves notice for its calls attention to a complex tumor of unknown pathogenesis with different criteria for histopathologic and hematologic diagnosis of the recognized entities. Failure to recognize lymphomatoid diseases as everchanging processes requiring repeated biopsies of tissue and repeated studies of the blood through the clinical course has delayed the adoption of a uniform classification of the many types of abnormal lymphoid reactions. McGavic's paper dealt with 21 verified cases in an effort to contribute toward a working basis for the management of patients with lymphomatoid diseases of the eye. He classified his cases as to histologic type. The three most important types given were simple lymphoma or lymphocytic celled lymphosarcoma, giant follicular lymphosarcoma and reticuline cell lymphosarcoma. Repeated differential blood counts in studies of the bone marrow were necessary to rule out or demonstrate leukemic changes.

The general outlook for patients with lymphomatoid disease is poor. With treatment approximately 15 per cent survived a five year period of observation. Lymphomatoid growths are radiosensitive but this quality must be differentiated from radiocurability. A given lesion

may be treated to complete regression but this does not preclude the appearance of tumor masses in other sites. The use of radiation in the region of the eye is, of course, a threat to the eye.

McGavic reported one case diagnosed as pseudo-tumor (granuloma of the orbit) on biopsy specimen which subsequently developed generalized lymphadenopathy. On biopsy of a supra-clavicular lymph node the diagnosis of a reticulin celled lymphosarcoma was made. In reviewing the case, McGavic stated that the disease was a changing lymphomatoid process but first appeared to be inflammatory.

I have a patient under observation at the present time with exophthalmos which was diagnosed pseudo-tumor on biopsy specimen, but who has diffuse lymphadenopathy of the adjacent preauricular and cervical nodes and enlargement of the maxillary glands which, I suspect, will be proved to be lymphosarcoma. So far, this patient has shown some local response to radiation of the orbit.

Davis¹³ paper on "*Tumors of the Optic Nerve Associated with Recklinghausen's Disease*" is notable for its splendid review of the subject of tumors of the optic nerve. Gliomas and meningiomas are virtually the only primary tumors of the optic nerve. "The glial tumors start with an abnormal proliferation of the adult types of neuroglia of the nerve stem. After varying periods of growth the abnormal neoplastic neuroglia cells penetrate the pia with the formation of a gliomatous tumor in the sheath. Proliferation of the mesothelial cells of the arachnoid follows the glial penetration of the pia with the formation of a tumorlike mass in this portion of the nerve sheath. Later, intermingling of the proliferated cells from these two areas produces a complex histologic structure, the precise nature of which it is difficult to interpret unless earlier stages of the growth have been studied because histogenesis of the neoplastic cells has not been determined." Such types as spongioblastoma, spongioneuroblastoma, astrocytoma and oligodendryocytoma have been reported. According to Davis the outstanding feature of the neoplastic cells was excessive fibre formation within as well as without the nerve stem. The predominant cell types were astrocytes so that he designated the five tumors of his series associated with Recklinghausen's disease "astrocytomas."

Further, on the basis of his experience, Davis stated that tumors of the optic nerve probably belong to a systemic disease as originally suggested by Emanuel which is borne out by the simultaneous appear-

ance of multiple lesions in the central and the proliferated nervous system, by the fact that the tumors are bilateral at times, and further by the fact that multiple involvement of the nerve has been reported. The slow rate of growth and the relatively benign nature of the tumors are characteristic of other lesions associated with this syndrome.

Cushing's^{14, 15, 16} papers on meningiomas give a concise understanding of the origin and behavior of this less common tumor of the optic nerve. Most meningiomas arise within the cranium but since cell clusters of the archnoid are found in the sheath of optic nerve, they may be primary in the orbit. The case of Friedenwald¹⁷ was demonstrated to have arisen within the orbit. One patient in my series with a very large meningioma of the orbital portion of the optic nerve showed a normal optic canal and, at this time, fifteen years since the operation, continues to be well and to have normal vision of the other eye.

Because of the variety of usually unsuitable names which have been applied to various tumors, great confusion exists in the literature in regard to most. Ophthalmologists have persisted in the use of the term "cholesteatoma" for that type of congenital growth which presents a glistening white, nodular appearance and known as "tumeur perlee" by the French. Since this congenital tumor, arising occasionally in the orbit and more frequently within the cranial cavity, appears to have a different origin from those cholesteatomata found associated with middle ear disease, it seems pertinent that a distinction be made.

The indispensable criterion for the diagnosis of these lesions is the microscopic demonstration of epidermoid elements making up the walls of the tumor. We are logically forced to name the growth from its indispensable character and should use the term suggested by Critchley and Ferguson,¹⁸ that is, *epidermoid*. The usual gross appearance of these tumors is that of an irregularly lobulated, white, opaque, glistening ovoid or spherical mass, varying from 1 or less to 10 centimeters in diameter. The tumor is firm but friable and breaks easily on moderate pressure. On section it often gives the appearance of an onion, owing to its laminations. It may leave a fatty stain on the knife and a fatty rancid or fatty odor may be detected. The very old tumors become necrotic, especially in the center and cholesterol crystals are found in this necrotic debris. It is avascular and easily removable.

In the opinion of Horrax¹⁹ the difference between epidermoid and dermoid tumors depends upon the depth of the cell layer from which

the embryonal rest arises. If the cells are derived from the epidermis the resulting tumor is an epidermoid. If, on the other hand, the original cells arose from the dermal layer the tumor contains hair, sebaceous glands and other dermal elements and should be termed "dermoid." This opinion is opposed to that of Boestrom who felt that not the depth of the cell layer but the embryonic age of the cell rest was the determinant. The more primitive and undifferentiated the cells of origin of the tumor, the more likely they are to give rise to dermoid rather than epidermoid tumors. The latter must, therefore, arise from inclusions occurring later in embryonic life. Clinically the dermoids frequently bring about symptoms at an earlier age in the life of the patient than the epidermoids.

The cholesteatomas associated with infection of the middle ear cavity consist mainly of epithelial debris with fat, granulation tissue, leukocytes and cholesterol crystals and may simply be the accumulated heaping up of excessive desquamation and reaction to inflammation. Erdheim,²⁰ however, reported a typical epidermoid in the middle ear unassociated with infection. It may be that under the stimulus of the inflammatory process the back growth of the meatal epithelium through the tympanic cavity gives rise to dermoid formation. It is possible, on the other hand, that the tumor may be present in the middle ear as an epithelial rest and its presence predisposes the ear to suppuration so that the infection and tumor formation are discovered in association with each other.

Adrenal sympathicoblastoma or neuroblastoma²¹ is one of the commonest causes of exophthalmos in children and might well be mentioned here. This malignant tumor, which is invariably fatal, arises from an embryonal nerve cell derived from neural ectoderm and is the primary sympathetic cell. This tumor has the same embryonic origin as the medulla of the suprarenal gland and the adjacent sympathetic ganglions and may arise from either. The neoplasm arises more frequently from adrenal medulla but it may arise from embryonal sympathetic cells or sympathicoblasts anywhere in the body.

The tumor consists of small cells which have hyperchromatic nuclei, are polymorphous, contain little cytoplasm and lie in dense, new-formed connective tissue. The cells with delicate fibrils are usually densely packed or grouped to present the appearance of an embryonic ganglion of the sympathetic nervous system (Wahl). The cells may also form

a rosette, arranged around a central mass of fibrils. Among these cells, larger round cells may be found, with larger, pale, vesicular nuclei and a larger rim of cytoplasm. These were called embryonic ganglion cells by Lewis and Geschickter. Rosettes are found in approximately 50 per cent of cases and these and/or fibrils should be present for a positive diagnosis according to Leinfelder. Verhoeff wrote that these rosettes are quite different from the rosettes of retinoblastoma.

The ocular signs are preëminent in the diagnosis of the tumor. The occurrence of ecchymosis of one or both lids alone or associated with exophthalmos not only should suggest adrenal sympathicoblastoma but may be diagnostic of the disease. Sturtevant and Kelly emphasized the fact that ecchymosis of the eyelids and proptosis in infants and children should arouse suspicion of adrenal neoplasm. Seefelder stated that these two ocular signs are diagnostic of the source of the orbital metastases. In addition, papilloedema and temporal tumor are frequently found. The metastases to the orbit are probably hematogenous. In the "Pepper type" the outstanding symptoms are local and involve only the lower and periaortic lymph nodes giving rise to abdominal signs, especially to a large liver and metastases to various parts of the skeleton. The average age of cases of the Pepper type is two years and of the Hutchison or cranial type is four to five years.

Because of the limited time and the vastness of the subject assigned to me I could scarcely do more than mention several tumors which seem of special interest at this stage in the development of our knowledge. The reason for choosing these particular neoplasms is apparent in each discussion. But by these reasons, many other tumors could have been included. Malignant melanoma and retinoblastoma required discussion not because they are the commonest tumors of the eye but because recent advances have been made in our understanding and management of them. The series of cases of exophthalmos mentioned seems a fair sample of the great variety of conditions which may cause displacement of the eye. With the x-ray we are able not only to diagnose many causes of exophthalmos but also to differentiate, with some degree of accuracy, at least a few of the various tumors which occur in the orbit.

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SOME PUBLIC HEALTH IMPLICATIONS OF SELECTIVE SERVICE REJECTIONS*

The A. Walter Suiter Lecture

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I APPRECIATE very much this opportunity to discuss with this group some implications of Selective Service findings to the public health.

The New York Academy of Medicine is outstanding among professional groups for its scientific thinking and for its promotion of scientific medicine. Your organization is especially to be commended for its encouragement of postgraduate education and of public education on the advances as well as the problems of medicine. It has led the profession in emphasizing the preventive aspects of medical practice and the relation between public health and clinical medicine. The Committee on Medicine and the Changing Order reflects your consciousness of the problems associated with maladjustments between the science of medicine and the application of medical knowledge.

It is a particular pleasure to present as the subject of a Suiter lecture this discussion of the most recent findings concerning the health of our young people. Doctor Suiter's long career was marked by great interest in public health affairs. It is my conviction that our success in attacking the public health problems which lie before us will depend in large measure upon similar interest and coöperation on the part of large numbers of physicians.

There has been much discussion concerning the accuracy of Selective Service reports, as well as of their worth in evaluating the state of national health. I would like to review these data from a statistical viewpoint for two purposes: (1) to indicate their value as indices of health needs and achievements, and (2) to draw certain inferences with regard to future public health planning.

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The traditional objective of public health is disease prevention. Through the years, public health activity has been concentrated primarily on certain acute conditions in which the causal factors and the onset of disease are immediately related in time. Some of these efforts have been markedly successful. Typhoid fever, diarrhea and enteritis, malaria and yellow fever have been greatly reduced through the application of environmental sanitation; diphtheria and smallpox by immunization; pellagra by increased knowledge of nutrition. But many widespread causes of disease and disability among the population have remained untouched. Gradually, we have come to realize that public health responsibility must extend to the prevention or early discovery of diseases and conditions which are insidious at onset. This concept is developing as one of the goals of preventive medicine. Consideration of Selective Service findings points to some of the steps to be taken toward achieving this goal.

In any evaluation of Selective Service findings, rejection rates must be a first consideration. Examination standards changed frequently during the course of the war. Hence, rejection rates varied greatly. We find, for example, that in the pre-Pearl Harbor days of Selective Service (November 1940 through September 1941) more than half of all men examined (52.8 per cent) were rejected for military duty. The rates decreased markedly following the declaration of war, as the need for manpower became intensified. By January 1943, they had reached a low of 28 per cent. With the calling up of older men and previously rejected men during that year, the rates rose gradually to 42 per cent, but by May 1944, they had dropped again—that time to 31 per cent. It was in this last period, you will recall, that the minimum age for military service was lowered from 21 to 18 years, and that unusually heavy quotas were levied on local boards. By the middle of the year, however, the rates began to increase steadily, until by November they had reached 45 per cent.

These figures I have just given by no means show all the fluctuations in rejection rates which resulted from the various changes in qualifications for military service. Rather, they illustrate some of the difficulties involved in evaluating the level of national health in terms of acceptance or rejection for military duty. In short, the gross rejection rates tell only the proportion of individuals who did not qualify according to the standards of one particular period.

My conclusion is by no means new. Leonard G. Rowntree, Medical Director of Selective Service, in 1944 told the Senate Subcommittee on Education and Labor that rejection rates are dependent on too many factors to be used as criteria in adjudging civilian health.

"The incidence of all recorded defects," he said, "is a better index of the health picture. The latter is only limited insofar as all defects may not be recorded."

There is no question that prevalence rates are better than rejection rates for evaluating national health. To the limitation pointed out by Dr. Rowntree, however, I would add the differences in examining techniques at the various examination centers, the idiosyncrasies of the examining personnel and the attitudes of the examinees.

A comparison of Selective Service findings for November 1940, through September 1941, with that for April 1942 through December 1943, illustrates the effects of these factors on the reported prevalence of disease and disability.

In the first report, an average of about one and one-half defects were recorded for each man examined (1,583.3 per 1,000); in the second, one defect for each man. Between the two periods, the coding procedures were changed so that a complete list of defects was not always available in the second period. Since the defects were summarized in order of significance, the limitations of coding would result in the omission of less significant defects and account, at least partly, for the drop in rate.

The effect of such omission, together with the other factors I have mentioned, can be gauged by a comparison of rates for specific kinds of defects. For example, in 1940-41 when the coding was more complete and when flat feet were a cause for rejection, foot defects, with an average of 172 per 1,000 men, led the list of disabilities. By 1942-43, however, minor foot ailments were considered unimportant, and only 55 per 1,000 men were recorded.

Reporting of dental defects followed a similar pattern. In the first period these defects averaged 168 per 1,000 men and were second highest among all defects. In 1942-43, the incidence had fallen to 113 per 1,000 examinees. This drop probably was due to the failure of examining personnel to record all cases of carious or missing teeth, or to give dental defects sufficient precedence for inclusion in the coding, since these defects no longer were cause for rejection.

Like decreases also occurred in the prevalence of throat diseases, skin diseases and defects of the abdominal viscera, as the need for military personnel grew more urgent and examining physicians tended to concentrate on the more serious systemic defects.

While a great increase in the reported incidence of tuberculosis took place in the later period, the rise—from 10 per 1,000 men in 1940-41 to 19 in 1942-43—may be accounted for largely by a change in examining procedure. Chest x-rays did not become an examination routine until 1942, and it is reasonable to suppose that many cases of tuberculosis among pre-Pearl Harbor inductees passed through examining stations undetected.

On the other hand, reports of many important defects remained fairly constant in both periods. Eye defects, for example, varied only slightly. We also find little change in the reported prevalence of neurological diseases or of diseases of the lung (other than tuberculosis), kidney and ear. The answer seems to be that a large proportion of conditions in these groups of defects were outright causes for rejection. Therefore, reporting necessarily was fairly complete.

Mental disease, which was high among the more serious defects for both periods, was found in 68 out of every 1,000 men examined in 1942-43. Leading the list among these diseases were psychoneurotic disorders, psychopathic personality and grave mental or personality disorders. Since serious attention was given by examining physicians to evidence of mental disease in both periods, and since reports for the periods are consistent, it could be concluded that reporting and coding of the incidence of mental disease were fairly accurate throughout the war.

I have presented these comparisons to bring out the fact that the order of defects may have been closely associated with prevailing regulations for the rejection or acceptance of examinees for military service.

As we review these figures, we find little reason to doubt that the findings for 1940-41 more clearly approach the actual prevalence of defects, although how close that approach is can only be guessed. There also seems reason to believe that the figures present a fair picture of the prevalence of major defects—with allowances made for variations in examining techniques, in the judgment of examining physicians and in the recording and coding of defects. It likewise appears obvious that the many factors which influenced the recognition and recording of

secondary defects detract from the accuracy of the reports.

None of these factors, however, obscures the enormous volume of defects which were found to exist among Selective Service registrants. Errors are, largely, errors of omission. Therefore, even the highest rates probably understate the true situation.

To students of national health problems, these findings represent no new discovery. The wide publicity and attention which Selective Service findings have attracted results, probably, from the quantity of defects reported. Health data have never before been obtained on such large numbers of young men; but numerous surveys have revealed the same basic facts.

An example of these surveys is to be found in the study conducted in 1941 among about 150,000 young boys and girls between the ages of 16 and 24 years who were employed by or seeking employment with the National Youth Administration. Physical examinations were conducted by private physicians, and persons requiring treatment were referred to physicians, clinics, hospitals or health agencies. The survey, which covered both urban and rural youth in 47 States showed that about one-third of all those examined had some health defect which placed some kind of restriction on the kind of work they could do. Three per cent of all youths examined were judged to be either temporarily or for a prolonged period unfit for any regular NYA employment.

But while only one-third were limited in their employability, about nine-tenths of the entire group were found to have one or more health defects. One hundred and sixty-six impairments were found for every 100 youths examined. Dental defects were highest—84 for every 100 youths. Eye defects were found to exist in 36 per cent of the group; bad tonsils in 19 per cent. Organic heart lesions were discovered in 2.5 per cent; orthopedic defects in 5 per cent; kidney conditions in 8 per cent; hernias in nearly 2 per cent.

As you will observe, the findings of this survey bear great similarity to Selective Service reports.

Both of these sources of information on the national health status cover only the younger segment of the population. There have been other studies, however, which have been directed to all age groups. The largest of these was the National Health Survey of 1935-36 in which an effort was made to determine the incidence and duration of illness over a period of time. While the study included analysis of all

types of illness, its findings on chronic diseases seem particularly pertinent since these, for the most part, are the serious diseases which attack persons of all ages. It was estimated, on the basis of this survey, that 25 million persons suffer from some disabling or non-disabling chronic ailment.

All of these surveys reiterate the indications of Selective Service findings that there is an enormous amount of defects among the population. While we are aware that rates based on Selective Service reports do not give us a complete accurate measure of the prevalence of defects, they do provide a fairly clear picture of the amounts and kinds of defects existing in our young men. It would seem appropriate, therefore, to compare these data with those collected in World War I in order to determine what change has taken place in the prevalence of physical impairments.

Selective Service figures for 1917-18 show that 662 defects per 1,000 men were recorded in contrast to 1,000 defects per 1,000 men in 1942-43, and 1,583 in 1940-41. Just as we found the differences between 1940-41 and 1942-43 to be due largely to the coding of the diseases, so it must be suspected that failure to record many minor defects in World War I accounts for a major part of the difference in the records of the two wars. In addition, differences in the medical terminology of the two periods make it difficult to determine the exact classification of defects in many instances. It must be remembered also that diagnosis of a number of diseases underwent refinement in the interval between wars.

As a result, although wide variations in some general groupings will be noted, in specific categories, where similarity in terminology permits comparison in the two periods, differences are not always as great as might be expected. Among diseases of the eye, for instance, 61 defects per 1,000 men examined were found in 1917-18, against 123 in 1940-41. Yet, for bilateral and unilateral blindness—an easily defined defect which can be assumed to have been reported in the same category for both wars, the difference is small. Similarly, there is only small variation in recordings of the incidence of trachoma, and the slight decrease noted in 1940-41 may point to some public health accomplishment in the conquest of this disease.

Increased medical knowledge is a factor that cannot be overlooked in comparing the incidence of a number of defects. This is particularly

true of asthma, cardiovascular disease, and venereal disease. Since diagnosis of these conditions is much more frequent throughout the population today than twenty years before, it follows that recognition of the diseases among a selected group in 1940 should be greater than in 1917.

Variations in the incidence of tuberculosis are of especial interest, since examination procedures in effect in 1940-41 more closely approximated those of 1917 than in any other period of World War II. Moreover, the decline in prevalence rates for the two periods (24.7 and 9.7 per 1,000 men examined) bears fairly close resemblance to the drop in the national tuberculosis mortality rate between 1930 (113.1) and 1940 (45.9). Since the reported incidence of tuberculosis increased markedly with the inauguration of chest X-rays as an examination routine—moving from 10 in 1940 to 19 per 1,000 men in 1942-43—it seems evident that considerable tuberculosis went undiscovered both in 1917-18 and in 1940-41.

Loss of members is an obvious defect that cannot be influenced by any of the elements affecting reporting or diagnostic procedures; therefore, these figures can be accepted at face value. The great similarity in rates for this type of defect, as well as for others which are easily observed, leads to the conclusion that the prevalence of a number of defects in 1917 was probably about the same as in 1940-41.

The comparison does not reveal evidence of great improvement. While slight decreases may be indicated in the incidence of a few defects and diseases over the twenty year period, they are too small to be proof of progress.

This picture is markedly different from that presented by a comparison of mortality data for the same two periods. The national mortality rate decreased 3.1 per cent in the interval between wars. Among young men 20 to 34 years old, the death rate has gone down nearly 30 per cent. We have seen, however, that this reduction in mortality is not associated with a corresponding reduction in impairments.

The first conclusion, then, that we can draw from these data is that Selective Service findings, based on physical examinations, provide a valuable supplement to mortality figures as an index of national health. Statisticians have long been aware that death is by no means a sufficiently comprehensive measure of the extent of disease or impairment. Regardless of the accuracy and completeness of mortality statistics, they

furnish direct knowledge of only a few of the health problems of the population and, at best, inferential information about some others. In order to obtain actual information on the extent of health problems, then, it would seem essential that we establish the mechanism for maintaining a continuing health inventory of the population. To a limited degree, Selective Service findings for World War I and World War II have provided such an inventory. They have pointed to the weaknesses of our past methods for early diagnosis and treatment.

During the decades between wars, health department activities have been increasingly concerned with the development of personal services. This development is illustrated by well-baby clinics, by maternal and child health work, by dental health programs. Selective Service findings, however, show that the evolution from the relatively restricted functions of quarantine and sanitation has not been rapid enough to meet the public health needs of the population.

Perhaps if we were to cling to the narrower approach to public health work, we would claim that defects uncovered by Selective Service fall outside our responsibility. If we were to cling to a limited definition of preventive medicine, we would say that for a majority of these conditions nothing can be done. We would say that even with fluorination of water supplies, only about 50 per cent of carious teeth in children could be prevented. We would point out that we do not know how to prevent most heart disease and that, particularly, we have no methods of preventing or controlling rheumatic and congenital heart defects. We would contend that most hernias are non-preventable.

Such a concept, however, is not compatible with the modern scope of public health services. While we fully recognize the importance of environmental controls and of protecting the individual when the environmental control is not adequate, we are convinced that effective preventive public health effort also must be directed toward the prompt detection of disease in the individual. Such detection should come at the earliest possible stage. For many defects, this detection must come early in childhood if it is to be effective. This has been recognized, in theory at least, by health authorities for many years. In fact, the school health examination represents nearly the only existing mechanism for a continuing health inventory.

In many of our largest communities we have seen the development of school health programs designed to safeguard and improve the health

of our youth. On the basis of Selective Service findings, it is obvious that these programs have failed to do a complete job. Some indications of how they have failed can be seen from a study conducted by the Public Health Service from data on the school health programs of one community over a period of twenty years. Comparisons were made between the physical status of selectees from that community and the physical status of those same youths when they were children some fifteen years earlier.

The findings of this study indicate that many of the physical defects responsible for the rejection of men by Selective Service in World War II were evident in their incipency when these young men were children. A relatively large number of the selectees who were rejected for defective teeth and vision, for example, gave evidence of those defects when they were in elementary school. Many cardiovascular and hearing defects responsible for rejection were detected in childhood.

The findings also demonstrate that efforts directed toward school children can be successful in finding many types of defects. The organization of the schools, where all the children are together at one time, permits us to carry out systematic procedures with minimum effort and personnel. If properly directed, school health examinations can lay the groundwork for preventing the development of many disabilities which were revealed by Selective Service examinations.

However, even if every community made comprehensive school health examinations, only a relatively small part of the problem of discovering defects would be met. After all, the total school enrollment accounts for only about 15 per cent of the population. Some additional method would have to be devised to determine the actual amount of defects among the remainder of the people.

From a public health standpoint, the mechanism for a health inventory should be directed at early detection. This detection of disease is as vitally important to an effective program of prevention as a program of diphtheria immunization is valuable to the prevention of diphtheria. Early detection may not prevent the development of some diseases as effectively as the antitoxin prevents diphtheria. But it would give the physician an opportunity to apply all his skills at a time when they would be most successful in alleviating the conditions or retarding their disabling or fatal effects. Much ill health can be traced to our fail-

ure to develop the means of tackling the whole problem of disease at the time of inception or in the early stages.

Obviously, we must rectify this failure. I do not pretend that the task confronting us is easy or can be accomplished overnight. Nor do I think we can expect our present official public health agencies to offer the whole solution. Certainly, the health officer must have an important role in such an undertaking. But we must look also to the private physician to implement a program directed toward the early detection of disease.

In a recent monograph on "Medical Education and the Changing Order," published by your Committee on Medicine and the Changing Order, Dr. Raymond B. Allen writes: "Physicians of the future must be capable of taking their places as responsible leaders in the community and of viewing the problems of medical service dispassionately. Unless they recognize the right of every person to adequate medical service, the medical profession will degenerate to the level of a trade in which, as tradesmen, physicians will be concerned merely with the techniques of their trade. The medical profession cannot assume full responsibility for supplying complete medical service everywhere; . . . It is under obligation, however, to cooperate fully with voluntary and public agencies so that together they may create the economic and social conditions which make possible an adequate medical service for all."

During the war we witnessed this type of participation, particularly with respect to Selective Service. In peacetime, the same participation—to a lesser degree, perhaps—is observed in the clinics of health departments. But the development of a mechanism directed toward the early detection of defects will require greater participation in community activities and greater coöperation with health agencies on the part of private practitioners than has existed to date.

The value of early detection of disease and defects has long been recognized. For many years, insurance companies have stressed the benefits to be derived from annual physical examinations and the prompt follow-up of early indications of disease. These companies have conducted extensive campaigns to convince their policyholders of the wisdom of such an approach to the problems of illness. It has been claimed that mortality rates have been reduced by these activities.

More recently, organizations established for the control of cancer,

tuberculosis, heart disease and other diseases have spent millions of dollars in nation-wide education programs to stimulate the public to watch for the early symptoms of these diseases. The Public Health Service, in coöperation with State and local health departments and the medical profession, has promoted the mass radiography technique for discovery of tuberculosis, and has assisted in its utilization on a community-wide basis.

Also worthy of particular note in programs for the early detection of disease are the Strang Memorial Clinic of the New York Infirmary and the clinics of the International Cancer Research Foundation. In the complete physical examinations primarily designed for the early diagnosis of cancer, many other conditions needing medical care have been discovered and the persons examined have been referred to private practitioners for treatment of the conditions detected.

Two months ago, I had the opportunity to observe at first hand the work being done at Peckham, London, toward the early discovery of disease. The Peckham experiment—as you probably know—is a bolder effort to tackle the problems of community health than has been attempted in this country.*

The origin of the Peckham plan goes back to 1926 when a small group of scientists and of young married people agreed to organize a health and community service. This service was to give the scientists an opportunity to make continuous studies of the growth and health of normal family groups. To the family groups it was to provide an opportunity to keep fit and ward off sickness before they became incapacitated. Each family agreed to pay a small weekly fee to support the service.

Over the years, membership has grown to around 2,000 families, and the small building which first housed the health center has been replaced by more commodious quarters. The development of recreational activities has been one of the methods employed to attract membership and to make the center a focal point in community and family life.

The primary accent on health, however, has been retained. A physical examination, or “overhaul” as the British call it, for each member of the family is a part of the enrollment procedure. This examination

* The project had to be discontinued for a time during the war but is now in operation again and building up its membership.

is repeated at regular intervals. In each case, the examination is complete, including laboratory tests, and is followed by a family consultation. As a part of the examination routine, all infants are seen each week, children 3 to 4 years old are examined every month, and school children every six months. No actual medical therapy is practiced, but members are put in contact with the proper agencies responsible for the technical part of rehabilitation.

These examinations are directed toward the discovery of defects and their relation to the physical efficiency of all family members in terms of the effect of health on capabilities for individual, family and social life. They have emphasized the importance of the pattern of growth and the need for continuous observation, and have thus developed valuable material for biological research.

Since the enrollment of the Peckham Health Center consists of "average" people who live in an area which has no particular social problem, British health authorities were somewhat amazed at the findings reported in 1940 on the physical examinations of 3,900 individuals of all ages in some 1,200 families. Ninety-one per cent were found on first examination to have some physiological defect, deficiency or aberration. In about two-thirds of these people, the disorder was masked by compensation, and therefore, the individuals considered themselves well. In only 32 per cent was the observed defect accompanied by disease.

In a report of these findings at Peckham, comparison was drawn with our own Selective Service reports.

"In 1941," the report states, "among the first batch of American recruits, 50 per cent were rejected as being unfit for admission to the U. S. Army, and in the opinion of authorities it is unlikely that more than 10 per cent of the rejects could be made fit for service. This indicates that the disorders found were not of a merely transitory nature, and leads to the conclusion that our findings are not peculiar to Peckham or even to the British Isles. It is a general, not a local phenomenon that we have encountered."

Let us examine more closely the lessons we can learn from Peckham and from efforts here at home to develop a community-wide approach to the problem of early detection of disease. In each instance, some method is employed to provide a center to which people can go for physical examinations. In each of these projects, an effort is made to educate individuals to the importance of finding out what is wrong

with them and doing something about it. In each instance, too, an attempt is made to utilize the facilities and skills of physicians in the community to discover and to correct impairments. At Peckham there is also a new note—the development of continuing records on the growth and health of the individual as part of the social unit.

In these attempts to stimulate early diagnosis and treatment of disease and defects, it seems to me we are developing a new role for the physician, a role which combines some of the functions of the health officer with those of the family doctor. To be effective on a community-wide scale, however, three things are necessary: (1) Adequate diagnostic facilities must be available for the physicians of the area; (2) all health information on each individual examined must be brought together and integrated; and (3) some means must be found to assure that each person gets the medical services needed to correct the defects revealed by the health examination.

I believe the creation of community health centers would greatly facilitate the early detection of disease in the population. Here, assembled in one place, could be located adequate diagnostic facilities for the use of all physicians in the area. Office space should be available for the practitioners of the area. Here would be a central place to which all members of the community could come in their efforts to maintain good health. Here, physicians could assist one another in offering the public the benefits of their combined medical knowledge. Here also, could be pooled the health records of all persons in the community.

I am convinced that this pooling is essential to a true evaluation of health conditions. Medical science has long appreciated the diagnostic importance of the history of the patient. More recent scientific developments, of which psychosomatic medicine is one, have shown that the history must go far beyond the medical record of the individual. It must include all the social and familial facts which have been demonstrated to play an important role in the development of disease. This full information is essential to the private physician in diagnosing and caring for his patient. It is likewise essential to the health officer in planning intelligently the health programs of his community.

I believe that this information would lead us to a better understanding of factors which favor the development of disease—particularly those of young adulthood and middle age. In dealing with research on the so-called chronic diseases, we are handicapped by the

great time lag which, apparently, exists between the period when the deleterious agents come into contact with the organism and the period when the disease is first manifest. We often do not know to what extent the factors favoring onset of disease are introduced in childhood or early youth. We do not know, for example, how soon in childhood begins that damage to heart muscles which is evidenced in cardiovascular disease in adult life. With a pooling of information on all possible factors affecting the individual, and the possibility of observing those individuals over a long period of time, we may be in a better position to determine the natural history of some diseases.

The final step in correcting defects, of course, is to make treatment available when need for treatment is indicated. Perhaps I have been discussing the implications of Selective Service figures too much from the point of view of the medical statistician, interested in his own particular brand of research and prejudiced by the statistician's urge to gather more and more figures. However, I am the first to realize that the figures deal with impaired individuals and that from the point of view of the individual and the community, we must do something more than count him.

The figures have been used, with some justice, as indication for the need of support of a whole host of specific programs ranging through school health, chronic disease, dental care, accident prevention, maternal and child health, psychosomatic medicine and many others. But for the very reason that the implications of the results cover the whole gamut of preventive and curative medicine, attention to any single aspect of the data can provide only a partial solution of the problem presented.

It is beyond the scope of this paper or the competence of its author to discuss in detail the elements of a program to reduce the volume of physical and mental defects in our population. Obviously it is a tremendous job involving the development of ways and means to bridge the gap between scientific knowledge and its practical application. Further, it means a constant striving, through research, to push forward the frontiers of scientific knowledge. The solution also involves facilities, personnel and money. There are differences of opinion as to details but there seems to be considerable agreement on the following elements of a national health program:

1. *Facilities and organization.* To realize to the full the benefits of modern medical science, there must be an adequate system of hospi-

tals, clinics and health centers so located that every individual in the nation is within reasonable distance of one of these facilities. There must be regional organization of facilities with two-way communication between them so that patients can go from the health center on the periphery to the medical center, if necessary, and physicians on the periphery can have the advice of consultants in the medical center or other parts of the region. Adequate diagnostic facilities must be available to every individual in the region. Complementary to the provision of facilities, group practice should be encouraged to the widest extent possible so that physicians can have the advantages of working together with common facilities and ancillary personnel.

2. *Education.* There must be education both of professional personnel and of the public. The scope of medical education must be expanded to the end that physicians become advisers on health both to the individual and to the community. Medical practice has been concerned too much with disease and too little with health. In addition to physicians, we shall need more dentists and nurses and auxiliary personnel. Public education will be necessary, both in matters of personal hygiene and to stimulate the public to take advantage of the available services. Education of professional personnel must include the preventive and social aspects of medicine with a realization of the concept expressed by the Goodenough Committee in Great Britain in its study of medical education: "The fact that this person has fallen ill may be due to causes associated with home conditions, his work, or even with the manner in which he uses his leisure; his recovery may be hastened or retarded by his mental state while under treatment, and his full restoration to health may depend largely upon what facilities for rehabilitation are available to him, and on the social circumstances in which he finds himself after cessation of active medical treatment."

3. *Research.* To make greatest headway with our problem, we shall need greatly expanded research covering a very broad field. This might be called Public Health research—research that includes but goes beyond purely clinical and laboratory research and considers man's social environment and heredity as they affect health. Further, there is the whole field of administrative research into the best ways and means of making available to the people existing knowledge for the control of disease and the promotion of positive health.

4. *Finances.* Last, and perhaps most important, is the question of

financing an adequate health program for the nation. Some of the services in such a program can and should be financed from general tax revenues; in the main, however, many people seem to agree that the majority of families with regular income would prefer to pay for their medical care. But unless some method of prepayment of the costs of medical care can be set up for them, these families will undoubtedly continue to postpone their medical examinations and health check-ups until they are sick. By that time their condition may well have advanced to a stage requiring such expensive and prolonged treatment that the family cannot meet its medical bills. As Dr. George Baehr said in a recent paper (*Recent Advances in the Medical Sciences; Their Application to Public Health*) before the 74th Annual Meeting of the American Public Health Association: "The debate has narrowed down to two alternatives: (1) Immediate nationwide adoption of a compulsory system of medical insurance, or (2) gradual experimentation in local areas in order to determine the changes in the methods of rendering medical services which may be required under a voluntary or compulsory prepayment plan."

Since the time of the Civil War, the high proportion of physical defects found among young men being examined for military service has been viewed with alarm. Almost the only result observable in eighty years, however, has been a number of papers by medical statisticians. In those eighty years, however, we have learned to pool our resources in the natural sciences and technology. It is only one step further to pool our medical skills and facilities to assure each child and adolescent the right to health—insofar as our knowledge can provide that health. The good health of the next generation rests in our hands. Planning for and establishing adequate health services for all the people of the nation offers a challenge to the medical profession, public health agencies, and community leaders. It is for them to assure that preventive, diagnostic, and curative skills are used to their maximum extent in a nationwide drive toward a first essential in the better life which each generation must provide for those to whom it must turn over its unsolved problems.

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BULLETIN OF
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AUGUST 1947

RECENT ADVANCES IN THE MEDICAL
TREATMENT OF HEART DISEASES*

PAUL D. WHITE

Clinical Professor of Medicine, Harvard Medical School

ONE HUNDRED years ago today on the 11th of February, 1847, Ellen Bouse, aged 34, entered the Massachusetts General Hospital under the care of Jacob Bigelow, then aged 60, and Oliver Wendell Holmes, then aged 38, because of severe pain and swelling of both ankles, both knees, both shoulders, and both wrists beginning one week earlier. Her skin was hot and her pulse rate was 120. Magnesium sulphate, elixir of opium, and fomentations of the painful joints were prescribed but she showed little improvement in the weeks that followed; in fact in some respects she grew steadily worse, with the development of nausea and vomiting and a "bellows murmur" coming with the first heart sound. As this murmur grew louder tincture of digitalis was given at a dose of 8 drops increasing to 15 drops every four hours except when there was vomiting or diarrhea. Other medicines and therapeutic measures included senna, aloes, colocynth, castor oil, jalap, rhubarb, soapsuds enemas, mercury, sodium and potassium tartrate, peppermint, cinnamon,

* Read before the New York Heart Association at The New York Academy of Medicine, February 11, 1947.

aconite, castoreum, spirits of nitrous ether, wine of colchicum, camphor inside and out, sinapisms to epigastrium and joints, blisters to the precordium and nape of the neck, and leeches to the temples and over the heart. Slowly she sank into a decline complicated by severe psychosis and on the 29th day of April she was discharged, in despair, I judge, by O.W.H. to the Insane Asylum, I presume McLean.

Twenty-five years ago on the 4th day of February, 1922, Helen McCarthy, 23 years old, entered the Massachusetts General Hospital because of dyspnea, palpitation, weakness, and swelling of the ankles without pain. Her initial diagnosis was auricular fibrillation, myocardial insufficiency, and right hydrothorax. Fourteen years earlier at the age of nine she had suffered an attack of severe chorea and one and one half years before admission constant palpitation set in. Seven weeks ago she grew much worse with dyspnea and moderate edema but treatment by rest and digitalis was followed by considerable improvement. Yesterday she suddenly became orthopneic and faint and was referred to the hospital. At entrance she was found to be slightly cyanotic with engorged neck veins, right hydrothorax, enlarged tender liver, edema of the ankles, and a much enlarged heart with systolic and diastolic murmurs, not otherwise described. The heart rate was irregular at 118 and the blood pressure was 110 systolic and 80 diastolic. She remained in the hospital four weeks with a fluctuating course but mostly down hill. There were three distinct febrile episodes lasting a few days at a time with leukocytosis, pleural pain, and X-ray evidence of pulmonary consolidation, called bronchopneumonia, as well as of pleural fluid. Blood cultures yielded no growth. Treatment consisted of chest tapping thrice, digitalization in full, morphine, codeine, acetphenetidin, triple bromides, veronal, neoarsphenamine twice because of the discovery of a positive Wassermann reaction, soft solid diet, and limited fluid intake. No diuretic therapy per se was prescribed and no diagnosis of probable recurrent pulmonary infarction or active rheumatism was suggested. On March 5th she was discharged it was said somewhat "relieved," but died at home four days later.

It is evident from these two case reports that considerable advance has been made during the last century and even during the last twenty-five years in the medical treatment of heart disease, but it has been slow and laborious. There is little or nothing of the spectacular growth and dramatic effects belonging to cardiovascular surgery about which Rob-

ert Gross, one of the ablest pioneers in the field, has just told us. Worth-while advances have, to be sure, been made in the understanding of heart disease and much ground work has been laid but the greatest advances in medical treatment of the causes of heart disease are still to come. God willing and with the world at peace they are very likely to arrive, at least some of those of major importance, within the next twenty-five years. I only hope that I may myself live long enough to see them—it will be a great day for us all, since the major causes of death, before old age comes, are still the cardiovascular diseases, in particular, the rheumatic, the hypertensive, and the coronary.

One of your own great leaders in New York, to whose name I would like to pay tribute, John Wyckoff, was one of the very first to follow the lead of Richard Cabot in pointing out the fundamental importance of classifying cardiac diagnosis by etiology as well as by structural change and functional condition. Simultaneously in New York and Boston the classification of heart disease which has now become “classical” was worked out and, simple though it is, has proved, I believe, to be the most important step made clinically in the management of heart disease. It has for over two decades now called attention to the preponderant need of treating and preventing the causes of heart disease rather than of concentrating on the therapy of damage already done and of the disorders of function arising therefrom wherein, as a matter of fact, our chief medical advances in recent years have actually been made.

We are thus only at the threshold of a new era of advances in the study of the causes of heart disease and of their treatment. We have progressed to the point where we do know what we need to learn. We also have the obligation to tell the public of our ignorance and yet at the same time of our hope that with their support we may forge ahead. Some things we have learned which can be applied at once through community effort but we must take care at the same time not to delude ourselves and others with false enthusiasm based on the frequency of heart diseases alone and on the idea that we can at once institute a campaign to control them all. We must take the people into our confidence and tell them how little we actually know about the chief causes of heart disease though at the same time we should urge their *patient support* of our future efforts, particularly in fundamental clinical and laboratory research. Fortunately the lay public is already interested and

sympathetic and is awaiting word from us about what to do. Also fortunately there are active associations of doctors and laymen of experience and wisdom who, after years of solid work of organization and study, are now ready to lead the way. The first major heart association in this country was organized right here in New York in 1915 and was called the Association for the Prevention and Relief of Heart Disease. Other pioneer groups were formed in Boston, Philadelphia, Chicago, and San Francisco. In 1924 members of these local groups met in St. Louis and organized the American Heart Association which is now the parent body with wide interests and new and extensive plans for the national coördination of all or almost all the groups and individuals at work on this great menace to the health of the nation. It is fitting that this meeting tonight to help inaugurate the new drive against heart disease should be held here in New York City which is both the home of the oldest local heart committee and the headquarters of the national association itself. I appreciate the honor and the significance of the occasion.

Now let me review briefly some of the recent medical advances in the treatment of heart diseases and follow that with the more important observations on what is still to be done. Let us start with the structural changes which until our generation constituted the great bulk of what was known and of what was discussed in the textbooks of the day: valvular and vascular deformities, cardiac enlargement, and pericarditis. We have made feeble advances medically in this area; surgery has done far better, in fact it is in this very field that surgical therapy has achieved brilliant results in the correction of congenital or acquired vascular anomalies, in the reduction of hypertensive cardiac enlargement by lumbar sympathectomy, in the drainage of pericardial sepsis, and in the resection of constricting pericardium.

Medically we can do nothing to correct deformed valves or blood vessels although so-called functional or relative valvular insufficiencies can on frequent occasions be cleared by improving myocardial tone in the course of treating heart failure by digitalis and otherwise. At this point I would like to interpolate the story of a patient who has shown us what an important role natural recovery may play in the clearing up of signs of heart disease, that is, in its reversibility. A lad 14 years old was seen and followed for rheumatic heart disease in the Children's Heart Clinic of the Out Patient Department of the Massachusetts Gen-

eral Hospital 23 years ago. He had had rheumatic fever, his heart was somewhat enlarged, and he showed typical mitral systolic and diastolic murmurs. The latter murmur was so pronounced that none of us (and several experienced cardiologists were involved) had any hesitation in diagnosing considerable mitral stenosis. This was the period when mitral valvulotomy was being carried out in a series of patients in Boston. Because of the threat of the future and of the apparent suitability of this patient for the operation it was agreed by all concerned that it should be carried out. Accordingly a date was set but an acute upper respiratory infection caused postponement. The boy was sent home to wait but never returned for the operation. Although he was followed up in a desultory way in the years succeeding, the full significance of the lesson he taught us did not attract our attention until about three years ago when at the age of 34 years, twenty years after our original study of him, this patient entered my general medical ward at the Massachusetts General Hospital with pneumonia. He quickly convalesced under chemotherapy and before discharge was appraised for slight (grade 1) apical systolic and diastolic murmurs without any cardiac enlargement at all. It then turned out that he was the same patient who had been diagnosed as having pronounced mitral stenosis 20 years earlier. What had happened was then clear as the result of other, though less striking, lessons which we had learned in the intervening 20 years. At the time of our first examination this boy had been suffering from active rheumatic myocarditis unrecognized by us and had a dilated left ventricle responsible for most if not all of the mitral murmurs heard at that time. Slowly the activity of the rheumatism subsided and with it the cardiac enlargement and murmurs; it is probable that the slight mitral systolic and diastolic murmurs that were found 20 years later were due to minimal residual deformity of the mitral valve which need cause neither disability nor shortening of life if further rheumatic fever can be escaped.

The one other type of heart disease that much more frequently and dramatically can reverse itself is that due to coronary artery narrowing or occlusion; here no matter as a rule what therapy we apply, aside from common sense measures and patient waiting, a large proportion of cases improve or even recover entirely through the development of an adequate collateral coronary circulation or the healing of myocardial infarcts. This possibility of spontaneous recovery from rheumatic and

coronary heart disease must ever be borne in our minds lest we delude ourselves into overconfidence as to the effect of various drugs and other therapeutic measures; on the other hand, it should not discourage or prevent us from constantly seeking better and more specific treatment.

That part of cardiac enlargement composed of dilatation, which so often is the chief reason for increase in heart volume, can often be lessened by medical treatment of which more anon. The same is true in some cases of hypertensive cardiac enlargement by either surgical or dietary treatment of the hypertension or quite likely by prolonged rest; possibly even the heart weight may be reduced by a decrease of the hypertrophy itself but of that we have no proof.

The medical treatment of acute bacterial pericarditis has of recent years advanced a good deal through the introduction of chemotherapy; even tuberculous pericarditis may thus, we hope, be some day controllable. With such specific treatment of the acute and subacute infections of the pericardium, chronic constrictive pericarditis should, in the course of time, become more and more of a rarity. What I have just said about bacterial pericarditis applies also to acute and subacute bacterial endocarditis which now can be stopped in the considerable majority of cases by chemotherapy before the valves, already deformed congenitally or by rheumatism, are further damaged.

From these small triumphs of the medical treatment of structural changes in the heart let us see what has been accomplished in the medical treatment of disorders of cardiac function, brought into the limelight a generation ago by Mackenzie, Wenckebach, and various other leaders in the study and treatment of heart disease. Myocardial weakness and failure have been handled more and more effectively with each passing decade, but the progress has not been rapid enough to be dramatic. In the first place 25 or 30 years ago there was a return to William Withering's excellent advice about digitalization so clearly presented in 1785. At the same time or soon thereafter came the important recognition of the great value of the maintenance of the full digitalis effect by the giving of daily rations. I can well recall the beneficent change resulting from this soon after my hospital interne days—we no longer saw the numerous cases of acute heart failure enter the emergency ward because of the wearing off of the effects of the customary so-called course of digitalis given a month or two earlier. A further advance that has come slowly in this country is less dramatic but in the

long run, I believe, sound, namely the introduction for routine use of the purer preparations of digitalis, the glycosides such as digitoxin which can be used directly by weight without the bother and uncertainty of animal standardization.

Next in the line of advances in the medical treatment of myocardial failure in our time was the improvement of diuretic therapy. Mercury had, to be sure, been used by mouth for generations as a vigorous diuretic but the refinement of the mercurials that can be given by vein or intramuscularly was certainly a step ahead, supported by acid producing or sodium extracting salts like ammonium chloride by mouth. At first such therapy was often limited to cases of obvious dropsy, but quickly it was realized that even left ventricular failure with dyspnea in attacks or on effort with or without evident pulmonary edema can be greatly benefited by occasional doses of mercurials or by the constant use of ammonium chloride. There are two bits of advice about diuretic therapy that in passing I would like to interpolate. In the first place, small doses of the mercurials may suffice to produce adequate diuresis without causing extensive dehydration or exhaustion—quite often I have found that $\frac{1}{2}$ cc. of mercurhydrin or mercupurin is better than the 2 cc. customarily given. In the second place, it should be remembered that it is possible to go rapidly from the frying pan into the fire, that is, from the one extreme of dropsy to the other extreme of dehydration with sodium depletion and even death. Too abrupt a change in body chemistry is doubtless unwise. I remember to have seen such a change thirty years ago after too vigorous a diuresis with mercury by mouth; and I have seen the same thing happen only thirty days ago after mercury by vein.

A third important advance in the medical treatment of congestive heart failure has been long in the making but only recently has it come into general use. That is the low sodium diet. Some salt restriction had been advised and practiced for many years but merely half heartedly. It was only when it became recognized that every single fraction of a gram of sodium chloride ingested in twenty-four hours might make the difference between success and failure, and that the amount of water ingested didn't matter at all (except that it should be adequate rather than limited) that a new and happier regime for the water or rather brine-logged patient began. He now could do with less of the troublesome mercurial injections, he was no longer thirsty, and he

could often increase his activity. To be sure a sodium chloride intake limited to 1.5 grams daily renders a diet unpalatable but it can be tolerated for a little while until such restriction is no longer necessary. As in the case of mercurial diuresis, so here too, especially when mercurials and the low sodium intake are combined, there can be too much of a good thing.

The last few paragraphs present some of the soundest and most commonly used medical measures introduced in recent years in the treatment of heart disease but they are after all desperate measures, that is, treatment directed to the end results of heart disease. They are, of course, essential and do prolong life somewhat and at the same time do render the last days or months or years more comfortable. No longer do patients die in the distressing dropsical states that I can in my earlier years so well remember; some complication now, like pulmonary embolism or infection, is likely to end the tale. Any boast, however, of our ability to render the last days of our cardiac patients more comfortable and more numerous is in feeble contrast to our inability to prevent or to stop the diseases that so seriously affect the heart. To those I shall shortly come.

The other common disorders of function against which we have advanced in our medical treatment are the arrhythmias. Mackenzie had only digitalis for auricular fibrillation and flutter and bromides for extrasystoles and paroxysmal tachycardia. Quinidine came into use after the first World War and is still commonly employed with effective results by many physicians who are familiar with it. During the shortage of the commercial drug made from the Javan cinchona bark during the second World War a synthetic quinidine was made from quinine and this has been shown to be as effective as the commercial quinidine. The efficient use of digitalis remains, however, the drug of choice in many cases of auricular fibrillation and flutter, not to restore normal rhythm but to reduce the ventricular rate to a reasonable level. For long or exhausting paroxysms of regular auricular tachycardia the cholin derivative mecholyl has frequently been effective through its vagal effect, the excess of which can be avoided by the emergency use of atropine. For the Adams-Stokes syndrome, epinephrine parenterally, introduced by Parkinson, remains the drug par excellence though some effects can be obtained by the use of ephedrine, paredrine or even on occasion, atropine.

Now we come to the real problem, namely, that of the treatment and prevention of the underlying causes of heart disease. If we include every factor which affects the heart harmfully at all, the causes of heart disease would be legion, but there are really only a few that are responsible for the very great percentage (95 per cent or more) of clinically important cases of heart disease; it is in our present discussion quite unnecessary even to list the numerous conditions like mumps or influenza which can in very rare cases seriously involve the heart. The important causes of heart disease are congenital deformities, rheumatic fever, bacterial endocarditis, diphtheria, syphilis, hypertension, and coronary arteriosclerosis. Two of these are certainly on the decline, diphtheria and syphilis, in large part, of course, because of their early recognition and increasingly more adequate treatment. In fact the former is almost, though not quite, nonexistent; it flared up a bit in the recent war because of the late treatment of some cases of skin diphtheria. The latter, syphilitic aortitis, has become not only much reduced in communities where syphilis itself is under better control, but after it has become evident in middle age it is now generally agreed that active though careful antisiphilitic treatment holds it in check and in some cases even seems to cure it.

I have not listed thyrocardiac disease at all, for during the last decade it has become almost extinct, at least in communities where thyroid disease is early recognized and adequately treated by surgery or otherwise. I see about one new case a year now, usually in an elderly woman who has suffered for years from a rather low grade chronically active but unrecognized thyrotoxicosis. Twenty odd years ago serious thyrocardiac disease was not rare with its auricular fibrillation and cardiac enlargement and failure. It was in that group of cases that Lahey and Hamilton made history in the demonstration of the reversibility of heart disease by surgery consisting of subtotal thyroidectomy.

A few words should be said about the problem of congenital heart disease. It is obvious that medically we can do nothing about it in the baby or young child in whom it is recognized, but there are some indications that we may be on the threshold of its prevention, in some cases at least. Gregg and Swan of Australia a few years ago reported the finding of multiple congenital defects, including cardiovascular anomalies, in infants born of mothers who suffered German measles during the first two months of pregnancy. We have ourselves encoun-

tered such cases but the complete story of how great the hazard is and about the effect of other virus diseases in early pregnancy has not yet been told. Prevention or early treatment of such diseases, if their incrimination is proved, may be the first important medical advance in this field, which at present remains almost entirely a problem for the surgeon.

Let us turn now to the brightest spot of all in the advance of the medical treatment of heart diseases in the last few years, namely the chemotherapy of bacterial endocarditis. Undoubtedly a good many instances of the acute variety are now prevented or early cleared by stopping the general infections, pneumococcic, gonococcic, streptococcic, or staphylococcic, that were once responsible for the great majority of cases of acute bacterial endocarditis. The treatment of the subacute variety of bacterial endocarditis, always more important clinically than the acute type, has undergone a dramatic change within our recent memory. About eight years ago the sulfonamides with much struggling reduced the mortality from *Streptococcus viridans* endocarditis from practically 100 per cent to about 94 per cent. This was a step ahead certainly and a forecast of a more hopeful future, but most of the patients still died. When penicillin entered the picture our spirits rose at first only to be dashed by the pessimistic early official report of the apparent failure of the drug in 17 patients. Soon thereafter there appeared the encouraging paper by Loewe which pointed the way to the dramatic success that followed. He showed that if enough of the drug is given the majority of cases of subacute bacterial endocarditis can be cured. The principle behind the success of this treatment is simple enough but it is often overlooked. It was behind the success both of liver treatment of pernicious anemia and of lumbodorsal sympathectomy for hypertension; the increase of the amount of treatment accounted for the success of each. Another lesson that we may derive from these experiences is that we must be constantly on the watch for individual accomplishments outside the rule of routine therapy; no matter if they seem at variance at first they may be proved of value by time and further trial. Now that international medical communications are again opening up after the second World War it is our duty to stimulate the exchange of information about diseases and their treatment throughout the world. There are many important things for us to learn about heart disease and its causes in every corner of the world. Is

hypertension, for example, really as rare in China as rumor has it? And if so, why?

Finally we have arrived at the crux of our problem, namely the medical treatment and prevention of the three commonest kinds of heart disease, the rheumatic, the hypertensive, and the coronary. If we can develop really adequate therapeutic measures against these three major causes of death we shall have succeeded in our aim today. But what can we actually do now? Truly very little. It is here in the most important aspect of our campaign against heart disease that we need the sympathy and the support of the lay public the world over. We need not only community planning but also support of studies of all kinds concerning these three major problems. We may somewhat empirically though effectively develop therapy to influence these vital factors, such as lumbodorsal sympathectomy for hypertension, but we must go deeper than that. We must get at the roots and then work more directly with our eyes open. Clues may be anywhere and therefore many different researches should be supported, both clinical and laboratory, and preferably the two combined in the best fashion of clinical investigation.

Fortunately the battle is well joined or at least started with respect to rheumatic heart disease. The soundly established Council on Rheumatic Fever has been backed by all the organizations and groups in the country especially experienced and interested in the subject. Its aims are manifold: to stimulate research, to coördinate existing knowledge, and to apply what is already known. It has been a long hard uphill fight but the active interest of many investigators in the future promises much. We are on the edge of answers to many questions. For example, what is the exact relationship of rheumatic fever to the hemolytic streptococcus infection which so often precedes by ten or twelve days the onset of rheumatism? Can we prevent rheumatic fever by preventing hemolytic streptococcus infections? If so, will chemotherapy or other measures of prevention or early treatment do the trick? What role does familial susceptibility play? Can rheumatic fever itself be checked in the future after it begins by something more effective than the salicylates? Positive answers to such questions as these will reduce or wipe out the chief cause of death in the second decade of life and the major cause of disability in young adults.

What now about hypertensive heart disease and the hypertension that causes it? One of the most dramatic experiences of my lifetime

has been my observation of the control of hypertensive heart diseases, which in some cases had progressed to the stage of actual failure of the left ventricle, by Smithwick's lumbodorsal sympathectomy. I assure you that this has not been an optical illusion on my part, for during the previous twenty years or more I had utilized the current medical therapy of the day with negligible or at best only palliative results *after the stage of serious hypertensive heart disease had developed*. Rest, restricted diets, and drugs such as the nitrites, sedatives, and thiocyanates had helped temporarily, though I had not, to be sure, employed the stricter low salt and rice diets which have shown of late on occasion a helpful effect, at least for the time being. But here in lumbodorsal sympathectomy was something which as a sceptic I encountered five years ago that did a different thing; in a large percentage of younger cases with adequate blood pressure reactions and renal function, good results, lasting for several years, have been attained whether or not the myocardium showed evidence of severe strain—in fact, other things being equal, the myocardial fatigue itself has been, in my experience, an indication rather than a contraindication, as in the old days, for the operation of lumbodorsal sympathectomy. But effective as it has often proved, surgical treatment of hypertension seems to me to be but a temporary makeshift; it is a difficult, painful, and tiresome, though in experienced hands, not a hazardous procedure. We must have something better eventually, both in prevention and in treatment, based on the as yet unknown causes of hypertension. Some drug, some diet, or some other simple measure, physiologically sound, will be the final answer. To date no long enough lasting adequate medical measure has, so far as I know, been discovered.

Last, but not least, in the catalogue of heart diseases and the one that most dramatically ends the lives of many important persons in the world at the very peaks of their useful careers, is coronary heart diseases. Like the rheumatic fever problem, so too both the hypertensive and the coronary problems deserve outstanding attention, even perhaps a formation of national councils for concentrated and coördinated work thereon, similar to that established for rheumatic fever. The crippling and often fatal effect of obstruction to the coronary blood flow by excessive atherosclerosis and intimal thickening is well recognized and its preponderance in the male sex in middle age and earlier is well known. Ten years ago Glendy, Levine, and I found that the ratio of males

to females with coronary heart disease under the age of 40 years was as overwhelming as 24 to 1. Here has been the most obviously neglected clue. We are studying now the anthropometric and metabolic findings in young "coronary" cases. Dock has pointed out the thicker coronary intima in newborn males as compared with newborn females. But we have just scratched the surface. We must learn much more and then apply scientific measures of prevention and early treatment to check the appalling waste of lives of useful persons. At present all we can do medically is to wait patiently with the help of restricted activity and the use of nitrites for the development of an adequate collateral coronary circulation or for the healing of a myocardial infarct. Most drugs and other measures of treatment that have been recommended in the past have not proved their worth, and surgery for the end stages of coronary heart disease hardly seems promising—we must begin at the other end. Every method of study of this vital problem the world over should be utilized including the geographic, racial and economic distribution of the disease. The life insurance companies in particular should take a leading part but the problem concerns us all, doctors and laymen alike. Whoever has a desire to aid in these important researches need but say so to any of us who are engaged therein, and such aid may be just the last bit needed to lead to a vital answer.

In closing, let me leave with you my firm conviction of the great value of the development of the community and national efforts about to be inaugurated in our struggle against heart disease, but at the same time let me emphasize our great ignorance of the causes and adequate treatment and prevention of all three of the major causes of heart disease; rheumatic fever, high blood pressure, and coronary artery obstruction. It is against these three foes of man that we must bend our greatest efforts.

CARCINOMA OF THE PROSTATE*

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WHEN Engelbach in 1888 collected 114 reported cases of malignant tumors of the prostate he did much to clarify the problem of obstruction of the bladder outlet. Even so, it was not before almost a quarter of a century had passed before clear cut differential diagnoses were generally made between benign and malignant prostatic diseases. Even though significant progress was being made, how primitive such a period now appears. Although our successors, principally because of greater knowledge of the steroid hormones, will be in a position to pity our floundering efforts to solve the problem, it is a fact that during the life of every experienced urologist now practicing, prostatic cancers and their proper treatment have become exceedingly important.

These tumors are not rare. It is recognized that of every 100 men who reach the age of sixty years, five will develop prostate cancers. In addition, careful microscopic studies of large numbers of prostates removed because of benign hyperplasia have shown unsuspected nests of cancer cells in approximately 20 per cent. Many ingenious methods of treating these tumors have been devised and skillfully performed; radical operations have been perfected by which not only the entire gland and its capsule but also the seminal vesicles and bladder trigone may be removed; radon and radium implants have been inserted in and about the tumor through the intact perineum, through the perineum with the tumor exposed and suprapubically through the opened bladder; roentgen therapy has been delivered by increasingly powerful units, but in spite of all efforts a cure was rarely achieved.

Surgery failed principally because prostatic cancers grow for a long time without causing any symptoms. When the tumor begins to obstruct the bladder and local symptoms insidiously develop, the disease, with few exceptions, has extended beyond reach of the most radical

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operation. Interstitial radiation, while sufficiently powerful to destroy the tumor in areas closely adjacent to the embedded seeds or needles, failed because of technical difficulties in placing the implants accurately throughout the entire growth. External radiation was unsuccessful because of the radioresistance of adenocarcinomas, the considerable distances of the prostate from the nearest body surfaces and the limitations placed on the method through fear of injuring the bladder or rectum. To illustrate the poor results produced by these methods even when carefully conducted, and to establish a basis of comparison with the results obtained by newer therapy, the statistics of the University of Michigan Hospital are of great interest.

TABLE I
From University of Michigan Hospital
END RESULTS OF 795 CASES OF PROSTATIC CANCER
TREATED FROM 1925 TO 1940

Number of patients followed	783
Patients known to be dead	737
Patients now living	46

Nesbit and his associates¹ studied the end results of 795 cases of prostatic carcinoma treated between the years 1925 and 1940 inclusive. They were able to follow accurately 98.5 per cent of all the patients in the group. As shown in Tables I and II, of the 795 men, 737 have died, 605 of prostatic cancers, sixty following operations, and sixty-seven of other known causes. Five patients died of unknown causes.

TABLE II
From University of Michigan Hospital
CAUSE OF DEATH OF 783 PATIENTS WITH PROSTATIC
CANCERS BEFORE ENDOCRINE THERAPY

Cancer of prostate	605
Operations	60
Other known causes	67
Unknown causes	5

Although 132 patients did not die primarily of prostatic cancers there is no reason to doubt but that they died with prostatic cancers and would have succumbed to this disease had no intercurrent illness supervened.

Against such a background of well deserved pessimism the announcement of Huggins² in 1941 was startling indeed. This investigator reported that men with advanced prostatic cancers could be benefited greatly by the simple operation of castration. Huggins' clinical work was based on a long series of ingenious animal experiments.³ Dogs' prostates were isolated from their bladders and a study was made of the normal excretion of prostatic fluid. It was then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown also that the administration of estrogens promptly stopped the production of prostatic fluid. It was learned that the administration of androgens caused hyperplasia of the epithelial cells of the prostate and that, in some cases, metaplasia became so pronounced that the appearance of the gland simulated cancer. When estrogens were given, these glands promptly returned to normal. Huggins also showed that after surgical castration prostate secretion stopped and metaplasia of the epithelial cells regressed. Although this work was by far the most complete and authoritative on the hormonal relationships of the prostate, earlier investigators had made a number of interesting observations.

Harvey observed that when the hedgehog hibernates the testes atrophy and the prostate also becomes smaller. He observed also that the prostates of bulls became smaller after castration. In 1893, White,⁴ on the basis of animal experiments, stated that the castration of dogs "was followed invariably and promptly by atrophy, first of glandular and then of muscular elements, of the prostate." Two years later the same clinician⁵ reported generally favorable results in a group of 111 patients castrated by him and others because of prostatic enlargement. In 1898, results were reported following the castration of a number of women for cancers of the breast. Although this treatment of breast cancer never proved successful, it did stimulate further the treatment of prostatic tumors by modification of the endocrines.

After a few years the treatment of prostatic enlargement by castration was largely abandoned. This was probably due to a number of factors. The majority of patients who visited physicians because of

bladder obstruction perhaps required relief more promptly than could be brought about by the removal of the testes; careful pathological differentiation between benign and malignant enlargements of the gland was not performed routinely; and finally, at this time there was greatly increased interest in the development of surgical methods for the relief of prostatic obstruction. For these reasons and perhaps others it was years before further attempts were made to control prostatic enlargement by endocrine methods. Beginning in 1934, Randall castrated five men who had prostatic cancers. Since it was necessary to relieve obstruction in each of these patients, transurethral resections of the bladder outlet were performed as well. Each of these patients followed a course which appeared to Randall to be what one would expect after transurethral resection alone. Therefore he did not report these operations until 1942. At about the time Randall's work was performed, or shortly later, Munger⁶ irradiated the testes of a number of men with prostatic cancers for the purpose of castrating them. He noted that these patients did better than his other patients treated by different methods. A number of competent urologists examined Munger's patients at various intervals after treatment and could palpate no evidence of prostatic carcinoma. Beginning about 1938, a number of investigators began to treat patients with prostatic carcinomas by administering female sex hormones by mouth and by pellets of estrogens inserted beneath the skin.

Another important phase of our subject is the remarkably rapid progress made in chemical laboratories through which tests were perfected to establish detailed diagnoses not only of the nature of the primary tumor but also of the extent of metastases. These tests were concerned principally in measuring the amount of phosphatases in the serum. Phosphatases are enzymes which split organic phosphates to give free phosphate ion. They fall into two groups according to the hydrogen ion concentration, (pH), at which they are most active. The acid phosphatases usually have a broad maximum of activity between pH 4.0 and 5.5, the alkaline phosphatases usually are most active in a narrow range between pH 9.0 and 9.5. Their exact properties depend on the tissue of origin and on the substrate used in measuring their activity. In 1935 Kutscher and Wolbergs⁷ isolated from the prostate a phosphatase which had its maximal activity in an acid solution. In 1936 the Gutmans and Sproull⁸ discovered that bones, the site of metastases from

carcinoma of the prostate, contained acid phosphatase in addition to the usual and well known alkaline bone phosphatase. In 1938 the Gutmans⁹ established the fact that there was but little acid phosphatase in the prostates of infants and that this substance increased greatly at puberty when testicular secretion began. These workers found acid phosphatase in the normal adult prostate, the hyperplastic prostate and the cancerous prostate. In 1938 and 1939 the Gutmans and Robinson showed that the acid phosphatase activities of the sera of many patients with metastasizing carcinoma of the prostate were greatly elevated. More recently, Gomori,¹⁰ through his microphosphatase tests, demonstrated that acid phosphatase was present only in the adult epithelial cells of the gland. This was the first exhibition of a secondary sex characteristic of a chemical nature.

Acid phosphatase occurs in many organs, but, with the exception of the prostate gland, no organ ordinarily contains more than one or two Bodansky units per gram of tissue. In the human adult prostate the acid phosphatase activity is high, reaching several hundred units per gram. The production of this enzyme by the prostate apparently requires androgens for its development and therefore does not occur before puberty. The acid phosphatase activity of prostatic carcinoma tissue is usually of the same order of magnitude as that of the normal prostate although it may be less in highly anaplastic carcinomas. Normal human serum contains small amounts of acid phosphatase. This cannot originate in the prostate since the activities of the sera of normal men are the same as those of the sera of normal women who have no organ which contains large amounts of the enzyme. At present the source of acid phosphatase in normal serum is unknown.

Woodard¹¹ made an important contribution in showing how often elevations in serum acid phosphatase occurred in patients with cancers of the prostate and in those with other diseases. Of seventy-one patients with cancers of the prostate and demonstrable bone metastases 51 or 72 per cent had elevated serum acid phosphatase. Of fifty-six patients with cancers of the prostate and no demonstrable bone metastases 19, or 34 per cent had elevated serum acid phosphatase. No elevations in the serum acid phosphatase have been found in patients with benign hyperplasia of the prostate nor in patients with cancers originating elsewhere which have invaded the prostate. This work and clinical experience appears to show that the acid phosphatase of cancerous

prostatic tissue does not enter the circulation as long as the capsule of the gland is intact. It may enter the circulation and be demonstrable in the serum as soon as local invasion or distant metastasis occurs and it does so somewhat more readily when metastases are in bone than in soft parts. In a few cases (probably not more than 10 per cent) elevations in serum acid phosphatase never occur even in the presence of extensive disseminated disease. In these cases it is possible that the tumor because of its structure produces little acid phosphatase, but additional autopsy material is necessary to prove this hypothesis.

Woodard¹² also assayed the serum of thirty-four women and 167 men who had osteogenic sarcoma, Pager's disease, jaundice of various types, plasma cell myeloma, lymphoma and other diseases not involving the prostate and failed to find any elevations of acid phosphatase. On the basis of this work she concluded that conspicuous elevation in serum acid phosphatase appears to be pathognomonic of metastasizing carcinoma of the prostate.

Many investigators have shown that alkaline phosphatase occurs in the kidney, intestinal mucosa, bones and some other tissues but only that from bones enters the blood stream in significant amounts. This enzyme is excreted by the liver and if this organ is diseased excretion may be impaired and the level in the serum may rise. Alkaline phosphatase production is increased as an essential part of new bone formation and with this activity there is a corresponding increase of the amount in the serum. Metastases to bone from carcinoma of the prostate, being nearly always osteoplastic, cause an increase of serum alkaline phosphatase in about 90 per cent of patients with metastases demonstrable and in some cases before any symptoms referable to bones have occurred. While unlike acid phosphatase, alkaline phosphatase is not specific for carcinoma of the prostate, in a patient without liver disease a rise in serum alkaline phosphatase warrants a strong suspicion that metastases to bones have taken place.

Because of the accuracy of phosphatase assays in showing the clinical status of patients, four reasonably clear cut groups may be recognized on the basis of these tests:

- 1) Normal men in whom there is no increase in either the serum acid or alkaline phosphatases.

- 2) Patients with proved cancers of the prostate and normal amounts

of both serum acid and alkaline phosphatases. In this small but important group one may perform radical surgery with a fair chance that the tumor has not grown beyond the gland.

3) A group consisting of the great majority of patients with prostatic carcinoma in whom the tumor has grown through the gland capsule with or without forming demonstrable distant metastases. In our experience the great majority show increased serum acid phosphatase.

4) Patients with prostatic cancers which have metastasized to bones. In this group both acid and alkaline phosphatases in the serum are elevated significantly. The amount of alkaline phosphatase in the serum so accurately represents the reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information regarding the immediate status of the patient not obtained by any other examinations such as roentgenograms. When both acid and alkaline phosphatases enter the serum from bone metastases the source of the acid phosphatase is the tumor in the bone while the alkaline phosphatase comes from the bone surrounding the tumor.

The improvement after castration of most patients with apparently hopelessly far advanced prostatic cancers is one of the most spectacular changes to be observed in clinical medicine.^{13, 14} The relief of pain from bone metastases probably is most gratifying and it usually occurs within thirty-six hours. Patients bed ridden for months because movements were agonizing and who had, as a result, developed serious contractures of their limbs may begin relearning to walk by the third or fourth postoperative day. Metabolism improves greatly, appetites often become ravenous so that men have doubled their body weight in a few months. Every laboratory test of fitness shows improved health. Improvement not infrequently is of such a degree that these men return to their usual occupations and may even resume activities in sports. Regression in the size of metastases to soft parts is usually prompt. Perhaps the most striking of these is the disappearance of large masses in the lungs, which has been observed many times. The primary tumor also shrinks after castration but at a variable rate and to a variable degree. In some cases one cannot detect any evidence of tumor by rectal palpation a few months after operation but usually regression is not so complete. If the patient had considerable bladder obstruction with correspondingly great quantities of residual urine transurethral resection of the bladder outlet usually is necessary. Roentgenograms of the skele-

ton taken at regular intervals have shown interesting bone changes but as yet we have difficulty in correlating the patient's clinical state with the bone pictures. We have seen patients, apparently much benefited by castration, in whom bone metastases seemed to be spreading. We have also observed what appeared to be improvement in a metastatic area in one side of the pelvis while, at the same time, an obvious metastasis in the other side became visible and grew. However, there is no doubt but that in some cases bone metastases heal, how frequently we do not know.

The testes removed from our patients grossly were normal. Microscopic study showed in practically all cases moderate tubular atrophy with from slight to considerable interstitial cell hyperplasia.

After enjoying greatly improved health for varying periods the men castrated because of advanced metastatic prostatic cancers begin to relapse and die. Usually the onset of relapse is characterized by a return of bone pains.

While observing the effects of castration on about eighty men another group of nearly 100 have been treated with female sex hormones administered by mouth.¹⁵ We have seen no clinical benefit from castration which has not been produced to as great a degree by estrogen therapy although improvement is not so prompt. Relief of pains from bone metastases which occurs so often within twenty-four hours of castration occurs only after estrogens have been given for from ten to fourteen days. The estrogen now used is ethinyl estradiol with the trade name of estinyl. The usual daily dose consists of two tablets, each of .05 milligram, taken on retiring.

Within a month of beginning estrogen therapy feminization of the patient appears. At first the nipples become tender, then the breasts enlarge. Later fat is deposited about the hips, the external genitalia shrink and finally a mons veneris is formed. The skin of the face assumes a finer texture and often the beard thins but it continues to grow. Libido probably is lost to a greater degree with estrogens than after castration, however, few of these patients were active sexually before treatment was started. Psychic changes are few and usually mild. A slight euphoria perhaps is most common. Maniacal states have been described following castration but there probably was instability before operation and a failure on the part of the physician to soothe and encourage the patient and obtain his consent. I have never had a patient

refuse castration and I have never felt compelled to tell him that he had a cancer.

As after castration, patients treated with estrogens often regain their previous physical capacities and carry on comfortably for variable periods when relapse occurs. In our experience there has been little difference in the length of time before relapse after castration or estrogen therapy. We have been able to give no appreciable relief to patients who relapsed after castration by administering stilbestrol, but since estinyl can be given in greater therapeutic quantities, trials with it are now being made although, as yet, they have not proved conclusive. In the same way, our patients who relapsed after estrogens have not been significantly improved by castration. Nesbit, however, reported a patient who failed to benefit from stilbestrol but who was completely relieved by castration. Such an occurrence must be rare.

Thinking it possible that androgen excretion by the adrenals explained relapses I removed both adrenal glands from three men who had relapsed after both castration and treatment with estrogens. None of these men lived more than four days and no further trials were made. Huggins performed the same operation on four patients with little more success.

It will be noted that the foregoing description of the striking response to castration and estrogens applies specifically to patients with advanced cancers of the prostate with bone metastases. Men with less advanced disease without bone metastases and bone pains do not show such prompt or profound benefit. In fact, Herger and Sauer point out that under apparently adequate estrogen therapy metastases develop in this group and they live no longer than patients reported by Bumpus¹⁶ who were in a similar clinical condition and who received no hormonal treatment.

The changes in the serum acid and alkaline phosphatases following modification of the endocrines are of both theoretical interest and clinical importance. When the serum acid phosphatase is elevated before treatment it usually shows a decided drop within a week of castration or within two to three weeks after the beginning of stilbestrol therapy. A more limited experience with estinyl suggests that the effect is similar to that of stilbestrol but further use of this drug may show slight differences. When the serum acid phosphatase is normal before treatment there is no immediate change after either castration or the ad-

ministration of estrogens. When treatment fails to initiate a prompt drop in the serum acid phosphatase the patient usually experiences no clinical improvement. These laboratory data corroborate the clinical observation of Herger and Sauer mentioned above. The presence or absence, therefore, of a prompt response of the serum acid phosphatase to treatment is of great prognostic value.

When a patient who has shown a drop in serum acid phosphatase with clinical improvement later relapses, the onset of clinical relapse, usually indicated by the return of bone pains, may or may not be accompanied by a significant increase in serum acid phosphatase. Sometimes the return of symptoms is preceded by a rise of acid phosphatase. When such a rise occurs it always indicates renewed activity of the disease. Unfortunately, persistence of normal values of serum acid phosphatase does not give assurance that the disease is under control. Probably discrepancies between the clinical onset of relapse and the time relapse is indicated by elevation of serum acid phosphatase are due to the fact that the most clear cut clinical evidence of relapse is the return of bone pains and this symptom may reappear at different stages in the depreciated conditions of different patients. The phosphatase assay, therefore, should be depended on as being the more accurate.

We have employed acid phosphatase assays in another way which has proved of considerable clinical value. Patients are occasionally seen with extensive inoperable tumors which involve the prostate and adjoining portions of the bladder or rectum. In such cases it is important to learn whether the growth originated in the bladder or rectum and invaded the prostate or whether it was primary in the prostate and later invaded the bladder or rectum because in the latter case great benefit may be obtained from endocrine therapy. Since prostatic cancers, even when they infiltrate other organs, contain comparatively large amounts of acid phosphatase, assays of tissue removed from the bladder with a cystoscope or from the rectum with a proctoscope have given a clear cut answer to the problem and have provided a rational basis for successful treatment in a number of cases.

The serum alkaline phosphatase in patients without bone metastases or liver disease is normal. This is not affected by endocrine treatment. As previously stated, the serum alkaline phosphatase is almost always elevated in patients with bone metastases from cancers of the prostate. In our experience within a month after surgical castration 80 per cent

of these men show a significant additional rise of serum alkaline phosphatase to amounts which sometimes become two to three times the initial quantities. When patients continue to have clinical improvement the serum alkaline phosphatase begins to fall after about three months and it may reach normal levels as the bone lesions become quiescent or heal. If clinical improvement is not sustained assays of this phosphatase usually remain high. When stilbestrol is employed only about one-third of the patients show a rise of serum alkaline phosphatase soon after the beginning of treatment. The remaining patients either show no reasonably prompt change when clinical improvement is lacking, or if the clinical response is good there is a gradual decline to normal values. Thus there appears to be a definite biological difference in the reactions of bone metastases to the two types of endocrine treatment.

Some work was done in the laboratories of the Memorial Hospital to show how the endocrines of patients with prostatic cancers were modified by castration or by the administration of stilbestrol. It will be remembered that Huggins³ believed, as a result of his experimental work with dogs, that the prostatic epithelium, whether normal or cancerous, was dependent for its growth on the relation of estrogenic to androgenic hormones in the blood. Estrogens demonstrably decreased prostatic secretion and androgens increased it in experimental animals. On this basis, therefore, the man with prostatic cancer was castrated for the purpose of removing the source of his androgens. It has been known for several years that men excrete estrogens in their urine. Since they have no ovaries their adrenals have usually been considered the source of these substances. It was thought that castration would not affect the adrenals and that the estrogens, therefore, would remain the same but that there would be a change in the estrogen-androgen relationship toward comparatively higher estrogen and lower androgen values. The administration of estrogens should also cause a similar shift in hormonal relations.

It was surprising to learn that these predicted theoretical changes were not borne out by our laboratory tests. Twenty-seven patients with prostatic cancers were studied in relation to their output of estrogens and androgens before and after castration. Before operation the estrogens averaged 16.6 mouse units per twenty-four hours and the androgens 6.1 milligrams of androsterone equivalent as determined colorimetrically

by the modification of the Zimmermann metadinitrobenzene reaction. Since a healthy young man excretes 15 to 25 milligrams of androgens in a similar period, it will be noted that our patients showed low 17-ketosteroid excretion. After castration, instead of estrogens remaining the same and androgens diminishing, the estrogens dropped in all but one of 16 patients to about one-half (8.5 mouse units) of the pre-castration level while the androgens remained the same or rose slightly (from an average of 6.1 to 7.1 milligrams in the 17 patients tested).

Gonadotropic hormones from the anterior pituitary gland were measured before and after operation in 16 patients. Of these, there was a definite post-castration rise in 11, while 5 showed quantities of this hormone too small to measure. In no case was there a decrease in gonadotropic hormone in the urine after castration.

Quite different from these reactions were those found by assays on 9 men before and after the administration of stilbestrol. Before treatment the estrogens of these men averaged 18.2 mouse units in twenty-four hours, while after treatment the quantity rose tremendously because a certain amount of the stilbestrol was excreted in the urine. The androgens before treatment averaged 8.9 milligrams of androsterone equivalent in twenty-four hours. After treatment these 17-ketosteroids fell in every case to an average of 5.4 milligrams of androsterone equivalent.

Of six patients in whom the excretion rate of gonadotropic hormone was studied before and after the administration of stilbestrol, in none was there a post-treatment rise.

From the viewpoint of hormones excreted in the urine, therefore, the treatment of prostatic cancer by castration differs greatly from treatment with stilbestrol. Castration seems to cut estrogenic excretion in half, tends to raise 17-ketosteroid excretion and to release the pituitary gland from testicular inhibition so that it puts out its gonadotropic hormone in excessive quantities. Stilbestrol raises the estrogenic excretion rate and decreases both the androgenic excretion rate and the quantity of gonadotropic hormone in the urine. It will be remembered that on the basis of phosphatase assays also bone metastases reacted differently to castration and to stilbestrol.

On the basis of present clinical and laboratory experience, therefore, it appears best to castrate the patient suffering pain from cancer of the prostate with bone metastases because in this way pain is relieved most

promptly. Castration also can be recommended for the patient who lives at a distance and would have no regular medical supervision. I also castrate those patients who I think would discontinue estrogens on becoming comfortable. Radical perineal prostatectomy still has an important place in treating those rare individuals whose prostatic cancers have not extended beyond the bladder neck or seminal vesicles. All other patients can be treated effectively, if they respond at all to endocrine therapy, by estinyl tablets taken by mouth. Two tablets daily of .05 milligram each usually are sufficient. While this drug in this dosage is well tolerated it seems best to have it taken on retiring. I have observed no especial benefit from large doses of estrogens before relapse has occurred, nor has there appeared especial efficiency in combining both castration and estrogen administration. The estinyl tablets should not be enteric coated because it is unnecessary and it prevents one from giving an accurate dose. From one of my patients who took thirty-five enteric coated estrogen tablets, twenty-two were recovered, apparently unchanged from the stool. I have had no personal experience in performing radical perineal prostatectomy on patients who were initially inoperable but who improved after taking estrogens, although Scott¹⁷ and Coulston, urologists of great experience and skill favor the procedure. No evidence has, as yet, been produced to indicate that the old belief of "once inoperable, always inoperable" is not true.

If relapse occurs under estrogen therapy, castration should be performed. While I have never observed significant improvement from such treatments, it is possible that at least one man, Nesbit's patient, was so helped. When relapse follows castration, estinyl in doses as large as tolerated is recommended. Since with this drug larger amounts of estrogenic hormone can be given without disabling side effects, its use in this way may have promise. Clinical trial in about twenty cases of castration relapse have appeared favorable but the end results are not known. Removal of both adrenal glands to relieve these otherwise hopeless patients has, as yet, proved impracticable. In an effort to depress the output of gonadotropic hormone put out by the anterior pituitary after castration, because there is evidence that this secretion may stimulate androgen production by the adrenals, high voltage roentgen rays have been delivered to the pituitary gland. No marked or protracted benefit has been observed after treatment by us or others such as Herbst,¹⁸ Herger and Sauer or Angrist and Khoury.

In studying the end results of five years experience in treating prostatic cancers by modification of the endocrines it is necessary to combine the reports of a number of observers because few clinics have treated sufficiently large groups of patients to have statistical significance. After treatment has been given, whether it was castration or the administration of estrogens, about 10 per cent of the men continue an uninterrupted downhill course which ends in death. The remaining patients, for the most part, are spectacularly improved. It is not possible at present to know how long this improvement will be maintained in the average case because a number of the patients treated earliest are still free from evidence of disease. However, about 65 per cent of those initially improved have since relapsed and have died. The average time that relapse occurred was thirteen months after treatment was started. The men who do not relapse within a year appear to have an excellent chance of remaining well considerably longer. While members of this more fortunate minority relapse from time to time, a small number have continued until the present in apparent good health, some with no evidence of disease. How long they can survive and whether they are truly cured is uncertain. One of our patients whose prostatic cancer was diagnosed histologically was treated with stilbestrol. He showed no evidence of tumor activity for four years when he died of coronary occlusion. An autopsy was performed and no gross or microscopic evidence of prostate tumor could be found, although sections were made of the entire prostate region. An occasional cure may therefore be possible.

Although remission of pain alone would justify the endocrine treatment of prostatic cancers the best statistics available show that the survival period of patients has been significantly prolonged as well.

TABLE III

*From University of Michigan Hospital***SURVIVAL PERIOD OF 735 PATIENTS WITH PROSTATIC
CANCERS BEFORE ENDOCRINE THERAPY**

Average survival of entire group 21.2 months
extremes 1 month and 15 years.

Average survival of 475 patients without metastases 24 months
extremes 1 month and 15 years.

Average survival of 260 patients with metastases 17 months
extremes 1 month and 176 months.

We are again indebted to Nesbit and his associates¹ in the University of Michigan Hospital, who, in studying their 795 patients treated without endocrine modification found that the average survival of the entire group was 21.2 months. Four hundred and seventy-five of the patients had no evidence of metastases at the time of diagnosis, and their average survival was nearly 24 months—the extremes being less than one month and 180 months (15 years). Two hundred and sixty patients had metastases at the time of diagnosis. Their average survival was 17 months—the extremes being one month and 176 months.

TABLE IV

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS NOT TREATED WITH ENDOCRINES AND THOSE CASTRATED OR GIVEN STILBESTROL.

Month	Control 781 Cases		Orchiectomy 75		Stilbestrol 50	
	No. Dead	% Dead	No. Dead	% Dead	No. Dead	% Dead
6	261	33.4	6	8.	1	2.
12	381	48.8	14	18.6	3	6.
18	483	61.9	22	29.3	10	20.
24	542	69.4	28	37.3	12	24
30	568	75.	32	42.6		
36	610	78.1	41	54.4		
42	637	81.5	46	61.3		
48	648	82.9	50	66.6		

Compared with this large group are two closed series of cases under endocrine treatment which are being followed until the death of the last survivor. One series of seventy-five patients had surgical castration while the other, of fifty patients received stilbestrol by mouth. Table IV includes all patients irrespective of their condition at the time of diagnosis. It shows that the death rate for endocrine methods was much less six months after treatment was started and after forty-eight months a considerable advantage was still maintained. No comparison of the two endocrine methods seems justified because of the small numbers in the two groups.

TABLE V

*From University of Michigan Hospital*COMPARISON OF SURVIVAL PERIOD OF PATIENTS
WITHOUT METASTASES

Month	<i>Control 388 Cases</i>		<i>Orchiectomy 45</i>		<i>Stilbestrol 33</i>	
	<i>No. Dead</i>	<i>% Dead</i>	<i>No. Dead</i>	<i>% Dead</i>	<i>No. Dead</i>	<i>% Dead</i>
6	106	27.3	2	4.4	0	0.
12	168	43.3	6	13.3	2	6.
18	211	54.3	8	17.7	4	12.1
24	233	60.0	14	31.1	5	15.1
30	255	65.7	15	33.3		
36	269	69.2	20	44.4		
42	288	72.6	23	51.1		
48	292	75.2	26	57.7		

TABLE VI

From University of Michigan Hospital

COMPARISON OF SURVIVAL PERIOD OF PATIENTS WITH METASTASES

Month	<i>Control 260 Cases</i>		<i>Orchiectomy 30</i>		<i>Stilbestrol 17</i>	
	<i>No. Dead</i>	<i>% Dead</i>	<i>No. Dead</i>	<i>% Dead</i>	<i>No. Dead</i>	<i>% Dead</i>
6	97	37.	4	13.3	0	0
12	149	57.	8	26.6	0	0
18	189	73	12	39.9	6	35.3
24	214	82	14	46.5	10	58.8
30	227	87.	17	56.5		
36	234	90.	22	73.1		
42	239	91.				
48	240	92.	23	76.4		

Tables V and VI also show increased longevity in patients treated by endocrine methods before and after metastasis has occurred respectively.

Even a brief review such as this shows that many investigators, studying different aspects of the problem during the past few years have added much to our knowledge of prostatic cancers and that as a

result the clinical course of many patients has been improved. Even so, only a beginning has been made. It has long been known that the clinical course of prostatic cancers depends to a great extent on their structure. Experience with endocrine therapy shows that tumor structure also strongly influences response to this form of treatment but, as yet, we are unable to correlate the two. It is also striking how uniform a pattern of end results is seen in each comprehensive group treated by modifying the endocrines but no less striking is the wide variation in the response of individual patients to the same treatment. At present knowledge does not permit individualized treatment for what must be many biologically different prostatic cancers but ignorance compels a repetition of practically the same empirical measures with each succeeding patient. With the realization of such present shortcomings it is gratifying to know that steroid hormone investigations now in progress in the laboratories of the Memorial Hospital promise to reveal clearly the one or more chemical substances which cause the origin and development of prostatic cancers. Furthermore, it is not too fanciful to predict that the time approaches when these guilty substances will be detected in young men and neutralized or destroyed before malignant changes in the prostate have begun.

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RESULTS OF PROSTIGMINE AND TRIDIONE THERAPY IN FIFTY CASES OF SPASTIC NEUROLOGICAL DISORDERS*

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THE effect of prostigmine therapy in several diseases in which muscular paralysis, tension, spasm, and painful cramps are prominent symptoms has been widely publicized during the past four years. Kabat and Knapp,¹ Geyerhahn,² Frankel,³ Fox and Spankus,⁴ and others have reported beneficial results with prostigmine in cases of poliomyelitis. They have observed relief from pain, relaxation of muscular spasm, and increase in strength and muscular coordination after treatment in the acute stages with this drug. Trommer and Cohen⁵ and Kabat⁶ reported good results in cases of chronic rheumatoid arthritis, and ventured the opinion that prostigmine was a far more efficacious drug in the relief of associated muscle spasm than any other drug previously used, including analgesics. Kabat and Jones⁷ widened the therapeutic applications for prostigmine by obtaining satisfactory results in the treatment of pain, spasm, and limitation of motion associated with such entities as subacromial bursitis, cervical intramuscular fibrositis, disabilities after fractures, and low back pain. An evaluation of the true therapeutic effect of this drug on muscle spasm per se has been extremely difficult in view of the fact that most series of treated cases have had intensive adjunctive physiotherapy.

It was postulated by Kabat and Knapp,¹ in their original work, that the site of action of prostigmine in cases of muscle spasm was in

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the spinal cord on the synaptic connections to the anterior horn cells, and not at the myo-neural junction, where its locus of action has been postulated in myasthenia gravis. Evidence to support this hypothesis has not been conclusive.

It would seem that if prostigmine relieves muscular spasm, caused by such distinctly different diseases as poliomyelitis, arthritis, and local muscular disorders, its usefulness might well be extended to the large number of neurological disorders in which spasticity or rigidity of muscles is an important, and often, disabling clinical feature. Schaubel⁸ and Jepson⁹ have treated cases of infantile cerebral spastic palsy with prostigmine, and observed encouraging results. (However, isolated instances of spastic neurological disease have been treated by us without obvious or convincing clinical improvement. In these few random cases, improvement followed only the institution of adequate physiotherapy, and seemed to occur independently of the drug therapy). The present study was, therefore, undertaken to give prostigmine therapy an adequate clinical trial in a wide variety of spastic neurological disorders.

In the pharmacological and clinical studies with tridione (3,5,5-trimethyloxazolidine-2,4-dione) it was observed that, in addition to its anti-convulsant and analgesic properties, this drug had "anti-spastic" effects similar to those previously observed with prostigmine. One investigator¹⁰ reported the use of tridione in 15 cases of cerebral palsies, of which five were of the extrapyramidal type and ten were of the cerebral spastic type; four of the five in the extrapyramidal group and seven of the ten in the cerebral spastic group were reported to show improvement in gait and ability to coördinate movements. In only two of the fifteen cases did the tridione appear to aggravate the condition. Perlstein and Andelman¹¹ in children with cerebral palsy, reported substantial improvement with tridione therapy, when the condition seemed to be associated with a psychogenic component. It was of little value, however, in relieving the involuntary spasticity or dystonia. Tetanic spasms were controlled by the intravenous administration of tridione. Chorea and postencephalitic Parkinsonism failed to respond in their series.

Since so few data exist as to the effect of tridione therapy on neuromuscular dysfunction, a companion study of the action of tridione on spastic neurological disorders was incorporated in the present investigation.

MATERIAL AND METHOD

Fifty cases of various spastic neurological conditions were studied. These fell into the following classification:

A. Hemiplegias (12):	
1. Cerebro-vascular occlusions	9
2. Intracranial neoplasms	2
3. Cranio-cerebral trauma	1
B. Paraplegias (9):	
4. Spinal cord compression	3
5. Vascular myelopathies	2
6. Traumatic paraplegias	4
C. Miscellaneous (pyramidal tract lesions) (13):	
7. Multiple sclerosis	6
8. Amyotrophic lateral sclerosis.....	2
9. Primary (?) lateral sclerosis.....	4
10. Subacute combined sclerosis.....	1
D. Extra-pyramidal disorders (16):	
11. Chronic Parkinsonism	13
12. Congenital extensor rigidity.....	1
13. Extra-pyramidal rigidity, etiology.....	1
14. Chorea-athetosis	1
TOTAL	50

Measurement of the response of muscle spasticity to each medication was formulated with difficulty at first, since it was not possible to use any known goniometer. Limitation of motion, usually measured by this instrument, was not a feature of more than half of the cases. However, with the end-point of obvious objective and subjective improvement in mind, the following simple criteria were conceived:

1. Passive resistance of the involved extremity.
2. Ability to walk without support.
3. Ability to walk a straight line.
4. Degree of adductor lower limb spasm.
5. Slowness of movement.
6. Ability to stand on one leg.
7. Tremor or other involuntary movements.
8. Subjective changes.

The degree of impairment for items 1, 4, 5 and 7 was listed as: 1'—none; 2'—mild; 3'—moderate; and 4'—severe. With associated weakness, ataxia, and involuntary movements varying with the type of neurological disorder, the primary criterion in which we were interested was passive resistance of the extremity. The other criteria depended too much on neurological disabilities other than muscle spasticity. Two other variables which had to be reconciled with the study were physiotherapy and spontaneous improvement. Heat, massage, passive exercise, and other physiotherapeutic procedures were continued during the course of drug therapy in sixteen of the fifty cases (32 per cent). These were distributed approximately equally in the different diagnostic classifications. Comparison with those cases not receiving physiotherapy was, therefore, possible should a noticeable difference in the response of the two groups occur. The well-known chronicity of the vast majority of neurological diseases included in this study diminished the possible error of spontaneous improvement. This factor was almost completely excluded by the over-all results in the series.

Method of Administration: A. Prostigmine*—This drug was given by the combined oral-parenteral route. Prostigmine bromide in doses of 15 mg. t.i.d. was given by mouth during the first three days of therapy, together with subcutaneous injections of Prostigmine methylsulfate, 1 mg. t.i.d. After three days, the oral dose was gradually increased in increments of 15 mg. until the patient was receiving 45 mg. t.i.d. by mouth and the continued 1 mg. injection, t.i.d., by the beginning of the second week of therapy. Atropine sulfate, in doses of 0.2 to 0.6 mg., was given only in those cases having side-effects from prostigmine. The duration of treatment in each case varied from three to six weeks. Shorter than three-week courses were used only in several cases of Parkinsonism, in which cases the drug was discontinued by the patient on his own initiative because of exacerbation of symptoms.

B. Tridione†—The oral preparation of tridione was used in all cases. Doses of 0.3 Gm. t.i.d. were given for one week. This was then increased to 0.6 Gm. t.i.d. for the next two weeks, and in some instances, for as long as the next four weeks. The duration of tridione therapy, therefore, ranged from three to five weeks.

Each of the fifty cases in this series received individual courses of both tridione and prostigmine therapy, although the duration between these courses in the same patient varied considerably: from two weeks to three months. Four types of response to each drug were recorded: 1) *Definite* improvement—if the degree of passive resistance and facility of movement changed 2 degrees or more, e.g.—from severe to mild, or from moderate to none; 2) *Slight* improvement—if the response changed only one degree, e.g.—from moderate to mild; 3) *No* improvement—with its obvious connotations; 4) Aggravation of clinical signs.

RESULTS

Table I illustrates the end-results of therapy with prostigmine. All twelve cases of hemiplegia failed to show improvement in passive resistance during the therapeutic trial. Since this group included nine cases of cerebrovascular lesions, some interesting variations existed. Three of the nine cases had flaccid hemiplegias at the beginning of therapy, having been quite recent vascular occlusions. Drug therapy in these instances was used in an effort to diminish or prevent the muscle spasticity which usually develops within the first two weeks after these occlusions, yet in two cases, muscle spasticity developed as would have normally been expected. In the third, the hemiplegia remained flaccid throughout the patient's hospital stay. Since a certain number of vascular hemiplegias ordinarily remain flaccid, depending on the site and extent of the lesion, this type of study with unpredictable variables, was discontinued.

No instances of definite improvement occurred with prostigmine therapy. Only three cases were recorded as showing slight improvement, one a case of cord compression from adhesive arachnoiditis, an-

* Supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

† Supplied by Abbott Laboratories, North Chicago, Illinois.

TABLE I
RESULTS OF PROSTIGMINE THERAPY ON MUSCLE SPASTICITY

<i>Case Group</i>	<i>Total #</i>	<i>Degree of Improvement</i>			
		<i>Definite</i>	<i>Slight</i>	<i>None</i>	<i>Worse</i>
A. Hemiplegias	12	0	0	12	0
B. Paraplegias	9	0	1	8	0
C. Miscellaneous	13	0	1	12	0
D. Extra-pyramidal disorders	16	0	1	7	8
<i>Total</i>	50	0	3	39	8

TABLE II
RESULTS OF TRIDIONE THERAPY ON MUSCLE SPASTICITY

<i>Case Group</i>	<i>Total #</i>	<i>Degree of Improvement</i>			
		<i>Definite</i>	<i>Slight</i>	<i>None</i>	<i>Worse</i>
A. Hemiplegias	12	0	1	11	0
B. Paraplegias	9	0	0	9	0
C. Miscellaneous	13	2	2	9	0
D. Extra-pyramidal disorders	16	0	0	5	11
<i>Total</i>	50	2	3	34	11

other a case of so-called primary lateral sclerosis, and the third an unusual type of extrapyramidal syndrome, either congenital or post-encephalitic in origin, and manifested chiefly by marked increase in extensor tonus of the lower extremities causing severe equino-varus deformities of the feet.

Of the 13 cases of chronic Parkinsonism (which included paralysis agitans, arteriosclerotics, and post-encephalitics), it was noteworthy that eight had severe aggravation of their symptoms: "stiffness". This required self-withdrawal of the drug. In half of these cases, the increase in severity of symptoms started during the five-day trial period after the cessation of all previous therapy, and was not relieved by prostigmine. In the other four cases, exacerbation of symptoms occurred during the course of prostigmine therapy.

The results of tridione therapy (Table II) were no more striking, but did include two cases, one of amyotrophic lateral sclerosis and another of primary lateral sclerosis, which clearly showed definite improvement during the four-week course of therapy (see Table II). Three other cases (hemiplegia from vascular accident, multiple sclerosis, and primary lateral sclerosis) showed slight improvement. The remaining 45 cases had either no clinical improvement in muscle tonus, or were decidedly worse during treatment. This latter group again included only cases of chronic Parkinsonism, eleven of which had to discontinue therapy on their own accord.

Complications were minor during each of the drug therapies. The gastrointestinal complaints associated with prostigmine therapy were easily controlled by judicious use of atropine. Four types of complications followed tridione therapy. Visual complaints (photophobia or hemeralopia) occurred in 50 per cent of the series. Marked leukopenia was not encountered in a single instance, although 18 cases (35 per cent) had significantly lower leukocyte counts at the completion of therapy, as compared to the pre-treatment counts. It must be remembered that the courses of tridione therapy were relatively short in this series, when compared with the use of tridione in the epilepsies. More pronounced decreases in leukocyte counts were, therefore, not expected. One patient presented the unusual complication of singultus which disappeared when therapy was stopped, recurred once when tridione was repeated, but did not recur on a third trial. During the third trial, however, an erythematous maculo-papular eruption developed over the patient's face and chest. One other patient had an episode of severe gastrointestinal complaints consisting of abdominal cramps and nausea, both of which disappeared within 24 hours after withdrawal of the drug.

CONCLUSIONS

Neither prostigmine nor tridione produced any significant therapeutic effect on muscle spasticity in fifty cases of various neurological disorders, with the common manifestation of demonstrable increase in muscle tonus. This lack of improvement is in sharp contrast to the reported benefits from prostigmine on muscle spasm associated with poliomyelitis, extremity fractures, rheumatoid arthritis, fibrositis, etc., and does not compare favorably with the results of prostigmine or

tridione therapy reported by some investigators in the management of infantile cerebral spastic palsy.

An explanation may be offered for this discrepancy of results. It is possible that the proposed hypothesis for the central action of prostigmine in cases of muscle spasm is in error, and that the drug acts in the usual manner at the neuromuscular junction, relieving spasm only when it is the result of increased muscle irritability on the basis of local inflammatory processes or reflex spasm from involvement of anterior horn cells. This type of action may not, therefore, be expected to relieve spasticity based on destruction of pyramidal or extra-pyramidal tracts in the central nervous system. There is the additional possibility that previous favorable reports of the action of prostigmine on diseases with muscle spasm reflect more the results of concomitant physiotherapy than of the drug action itself.

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CLINICAL MANIFESTATIONS OF
ADRENAL CORTICAL HYPERFUNCTION*

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DURING the past two decades many aspects of the functions of the adrenal cortex have been elaborated and clarified. In great part our understanding of the physiology of the adrenals has been the result of experimental observations associated with the removal of the adrenal glands. In this way we learned about the effects of the adrenal cortex on electrolyte and carbohydrate metabolism, on renal function, on growth of young animals, on resistance to stress, its relation to blood pressure and muscular response. In a sense, then, our knowledge has been achieved in a negative way in terms of things that happen to the body when it is deprived of adrenal cortical secretions.

With the isolation of active adrenal cortical hormonal fractions attempts were made to determine the effects of hyperfunction of the adrenal cortex on the body economy. These observations were only in part satisfactory. We know that the injection of certain of the steroid cortical fractions results in the retention of blood sodium and water, an increase in blood pressure, alterations in carbohydrate metabolism. but we have not succeeded in duplicating the clinical picture which we commonly associate with hyperfunction of the adrenal cortex. The basic blood chemical findings, the asthenia, the hypotension, the gastrointestinal symptoms, and the fatal termination of the bilaterally adrenalectomized animal are not dissimilar to the clinical picture observed in patients with Addison's disease. But the clinical adrenogenital syndrome cannot be duplicated by the injection of the available cortical hormones into the experimental animal. There are probably several reasons for this. The hormonal fractions that we have available are probably by no means the only ones elaborated by the adrenal. The system of endocrine balance operative in the normal individual or in the normal experimental animal is in all probability not affected by

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injections of cortical hormones in the same fashion as in the adrenogenital syndrome in the human where the adrenals or the pituitary are the seat of overt disease. It does not follow, however, that because we fail to duplicate the adrenogenital syndrome in the experimental animal with our available techniques that such a syndrome is not due to disease of the adrenal cortex.

Our studies then, concerning the role of hyperfunction of the adrenal cortex are dependent upon clinical observations in patients with demonstrable disease of these glands. The most outstanding clinical entity in this respect is the adrenogenital syndrome. Here too the observations are by no means clear cut. Although patients with an adrenal cortical tumor will manifest a certain clinical picture, similar if not identical observations are elicited in patients who have pathology elsewhere than in the adrenal. We attempt to explain this phenomenon in part at least by the influence of the other glands on adrenal cortical function and vice versa. There has been a good deal of speculation concerning the role of the adrenal cortex in the production of certain isolated clinical phenomena, such as hirsutism, perhaps hypertension, obesity, and menstrual abnormalities, but the evidence of such a relationship is not an entirely convincing one. We must, therefore, use the adrenogenital syndrome due to a tumor of the adrenal cortex or to hyperplasia of the adrenal cortex as the starting point from which to study the clinical role of adrenal cortical hyperfunction.

In a general way we may divide the symptoms of the adrenogenital syndrome into three large groups: 1) Those associated with premature sexual and physical development; 2) Those associated with signs and manifestations of increased or decreased virility; and 3) Those other symptoms which are part of the disease but are not manifestations or disturbances in sexual physiology. The first group includes the evidences of pseudohermaphroditism and precocious physical development. In the second category are the manifestation of male virilism in the female, and in the male signs of feminization. The third group includes the development of obesity, hypertension, glycosuria, osteoporosis, purplish striae, polycythemia, dusky cyanotic discoloration of the skin, acneform eruptions, and a tendency to purpura and ecchymosis. In a strict, legalistic sense the symptoms of the first two groups are referred to as the adrenogenital syndrome, while those of the third group are known as the Cushing's syndrome.

The clinical picture which patients with adrenal cortical hyperfunction will manifest is dependent in great part on the age at which such cortical abnormality occurs, and in part on the sex of the patient. In addition, however, there would seem to be no clear cut explanation at the present time as to why some patients will show predominantly the picture of an adrenogenital syndrome, while in others the major manifestations are those of the curious metabolic disturbances referred to as Cushing's syndrome, and a third group will show a combination of both. Histologically the tumor or hyperplasia found in one group is not distinguishable from that found in the other. But we must assume that not all of the adrenal cortical cells are hormone secreting cells, nor that all the cells secrete the same hormones at the same time. It is theoretically possible, therefore, that the different clinical manifestations are also due in some part to the different adrenal cortical cells with their different functions which may be involved.

It is worth emphasizing again that an identical picture may be produced by a tumor of the adrenal cortex, bilateral hyperplasia of the adrenal cortex, or in the presence of an ostensibly normal adrenal cortex associated with a tumor of the anterior lobe of the hypophysis. These pituitary tumors are usually basophil in character, but very occasionally they are made up of sarcomatous or undifferentiated cells. Finally, to add to our confusion, an identical clinical picture may be presented in the absence of any overt anatomical abnormalities associated with any of the endocrine glands. However, one consistent histological abnormality has been observed in the vast majority of patients with the adrenogenital-Cushing's syndrome. This is the curious hyaline changes in the basophil cells of the anterior lobe of the hypophysis so carefully observed by Crooke¹ and subsequently confirmed by many other investigators. The significance of these changes is by no means clear. Severinghaus and Thompson² succeeded in inducing vacuolar and hyaline changes in the basophil cells in the pituitary of the dog indistinguishable from those observed by Crooke in Cushing's syndrome. These changes were induced in one set of animals by the injection of crude sheep anterior pituitary extract over a prolonged period of time, and in another set of dogs by the injection of suitable anti-hormone serum. These authors concluded that the basophilic vacuolation is a characteristic retrogressive phenomenon which the cells undergo when their normal physiology is disturbed and the Crooke changes are re-

garded as an aspect of the general granule liquefaction which also appears after experimental thyroidectomy and after castration.

In the light of the clinical and experimental studies available it is difficult to believe that the cause of the adrenogenital-Cushing's syndrome is these Crooke changes. Rather it is a reasonable assumption that these changes are secondary to the disturbed adrenal cortical function and fall essentially into the same category as the other clinical signs and symptoms, such as hypertension, osteoporosis, and so forth. Similarly one is not impressed with the fundamental causative significance of the fuchsinophilic granules demonstrated in the cells of the adrenal cortex by Broster and Vines.³ This staining reaction has been observed by Cahill and his coworkers⁴ not only in patients with adrenal cortical tumors but in the adrenals of dogs and individuals without any manifestations of adrenal cortical disease.

What can we conclude, therefore, concerning the etiology of the adrenogenital-Cushing's syndrome? The frequency with which this disease is associated with some overt pathology in the adrenal cortex and the complete reversal of the clinical picture after successful surgical treatment of such adrenal pathology leads one inevitably to the conclusion that these glands play a vital role in the pathogenesis of this syndrome. Even in those instances in which the major pathology is located in the pituitary or hypothalamus the effect of such pathology in the production of the typical clinical picture is probably mediated through the adrenal cortex.⁵ The question of the clinical manifestations is in part dependent upon the time of onset of the adrenal cortical disease and in part on the sex of the patient. When hyperplasia or tumor of the adrenal cortex develops in utero pseudohermaphroditism will result. Pseudohermaphroditism is characterized by the presence of the gonads of only one sex, but associated with this are such abnormalities of the external genitalia as to render the identification of the sex through external examination doubtful. Male pseudohermaphrodites are those individuals whose gonads are testes, while female pseudohermaphrodites have ovaries. The classification into male and female pseudohermaphrodites is entirely independent of the nature of the external genitalia, and frequently final determination of the sex requires surgical inspection of the pelvic organs. True hermaphroditism differs from pseudohermaphroditism in that the former is characterized by the presence of the gonads of both sexes in the same person. True hermaphroditism is an embryo-

logical developmental defect and is in no way related to abnormalities of the adrenal cortex.

Marchand⁶ was perhaps the first investigator to point out the association of pseudohermaphroditism with hyperplasia of the adrenal cortex. This observation was subsequently confirmed by Glynn,⁷ and today we recognize that female pseudohermaphroditism is usually due to hyperplasia of the adrenal cortex occurring in utero and occasionally to adrenal cortical tumor. The pseudohermaphrodite does not present any other manifestations of the Cushing's syndrome, and pseudohermaphroditism is compatible with a long life span.

The development of an adrenal cortical tumor or hyperplasia in children before puberty may result in the production of precocious obesity, excessive muscular development, and marked sexual alterations. It was originally thought that the metabolic disturbances characteristic of Cushing's syndrome were rare in children with adrenal cortical disease. However, this is not so, and we now recognize evidences of this abnormality in these patients.⁵ The adrenogenital syndrome in female children is characterized by sexual precocity, the development of hirsutism of the face and limbs, enlargement of the external genitalia, and deepening of the voice. In most instances there is a temporary period of rapid growth which is, however, followed by an early closure of the epiphyses, so that the end result is usually a rather short individual. Menstruation as a rule does not occur even in older children who may have reached the age of puberty, although several notable exceptions have been reported.⁵ In general in both boys and girls the clinical picture is that of a rapidly aging process in which during the space of a few short months or years the child develops physically into an adult.

Such adrenal cortical disease in boys is characterized by obesity, marked muscular development, or both. The male children grow rapidly and develop signs of virilism with excessive hirsutism of the face, pubis, and frequently the rest of the body. There is marked precocious sexual development which, unlike that observed in girls, is homologous. The size of the genitals may assume adult proportions, although genital maturation is not necessarily associated with adult potency. However, spermatogenesis has been known to occur, and in at least one reported instance a boy of eight actually acquired a venereal infection through the usual channels.⁵

The development of this syndrome in children is more commonly associated with an adrenal cortical tumor than with adrenal cortical hyperplasia.

The clinical picture in adults is somewhat different from that observed in children. Women afflicted with the disease may manifest predominantly the adrenogenital syndrome, the Cushing's syndrome, or a combination of both. The latter is the most common clinical picture observed. The syndrome is seen more commonly in women than in men and may occur at any age between puberty and the menopause. Most instances are observed between the second and fourth decades of life, although some cases occurring after the menopause have been reported.⁵

The adrenogenital syndrome in women is characterized by virilism with the appearance of secondary male characteristics and the suppression of at least many of the female characteristics. They develop extensive hirsutism of the face, often with a well defined moustache and beard requiring daily shaving. There is usually an increase of hair over the extremities and over the pubis, the latter acquiring a male pattern. The hair may be fine and silky in character, or it may be long, coarse, and thick. Either directly before or coincidental with the hypertrichosis there occurs an alteration in the menses. They become scanty and infrequent and eventually cease entirely. Associated with this there occurs a diminution in libido and occasionally even a transfer of sexual interest to other females. There follows atrophy of the breasts and a decrease in chest and hip fat. Muscular development becomes more pronounced and the entire physical configuration tends to assume the male form. The clitoris may hypertrophy, and labia darken somewhat in color, and the uterus and adnexae tend to shrink somewhat in size. The voice deepens and becomes rough, probably due to thickening and elongation of the vocal cords. When there are associated evidences of Cushing's syndrome these patients will manifest in addition to the virilism, hypertension,⁸ a curiously distributed obesity, osteoporosis, moonlike facies, alterations in carbohydrate metabolism, purplish striae, and so forth. Occasionally the only evidence of adrenal cortical disease may be a very marked obesity.

Hormonal adrenal cortical tumors or adrenal cortical hyperplasia in the male are extremely rare. When they occur they generally assume one of two forms. Either they present the picture of Cushing's syndrome without virilism but with some loss of libido and a decrease in

size of the genitals, or they show actual signs of marked feminization with comparatively few manifestations of the Cushing's counterpart. Where feminization in the male has been very marked the pathology has generally proven to be an adrenal cortical carcinoma. In adult males, in contrast to prepuberal boys, the sexual abnormalities are characterized not by an increase in virilism but rather by the development of feminine characteristics.

In this general discussion concerning the symptoms of adrenal cortical tumors we have placed great emphasis upon the distinction between the sexual abnormalities observed and the metabolic aberrations characteristic of the Cushing's syndrome. This distinction is of considerable practical significance. The life span of the patient who shows virilism alone is considerably longer and the outlook very much better than is the case with the patient who shows evidence of Cushing's syndrome. In the latter group the contralateral adrenal is always atrophic, either grossly or functionally, and the operative risk associated with removal of the adrenal tumor is exorbitantly high. This is particularly true of the benign hormonal adrenal cortical tumors, in contrast to the malignant ones. The malignant tumors can often be removed with comparatively small operative fatality, probably because metastases occur early. These metastases constitute functioning adrenal cortical tissue.⁵ On the other hand, in our experience, and this I think is fairly uniform with some modifications, the operative mortality following the removal of a benign hormonal adrenal cortical tumor in patients with Cushing's syndrome is excessively high. In patients who present only virilism the contralateral adrenal is perfectly normal, and the removal of the tumor can be effected without any undue operative fatality. Where hyperplasia of the adrenal cortex is the cause of the syndrome such hyperplasia is bilateral and one adrenal can always be removed quite safely.

In view of the relationship of the adrenal cortex to electrolyte metabolism one would expect that this would be reflected in some fashion in patients with adrenal cortical hyperfunction. Since in adrenal cortical deprivation there occurs a reduction in the serum sodium and chloride with an increase in the serum potassium, it would seem that in hyperfunction of the adrenal cortex the direct antithesis of this might be observed. It is of great interest that such electrolyte changes are relatively infrequently seen in patients with the adrenogenital-Cushing's syndrome. Of forty-five well defined instances of this syndrome

TABLE I
FORTY-FIVE COLLECTED CASES FROM THE LITERATURE IN
WHICH BLOOD ELECTROLYTE LEVELS WERE RECORDED

	<i>Normal</i>	<i>Elevated</i>	<i>Reduced</i>	<i>Questionable Elevation</i>	<i>Questionable Reduction</i>
Na	38	4	0	3	..
Cl	40	0	5		
K	33	0	8		.

collected from the literature, in which adequate blood sodium, chloride, and potassium levels were determined, some abnormalities in the sodium ion values were found in seven instances, in chloride levels in five, and in potassium values in eleven instances. Where abnormality of the blood sodium has been evident, it has usually been characterized by an increase in this ion. The chlorides and potassium, on the other hand, if abnormal have usually shown a decrease in serum concentration. Kepler⁹ reported the occurrence of a reduction in the blood level of chlorides and potassium, a considerable elevation in the blood CO₂, and a normal concentration of blood sodium. McQuarrie and his group¹⁰ also demonstrated considerable alkalosis, reduction in the blood chlorides and potassium, but in addition in his patient there was a marked elevation in the blood sodium level.

It will be noted that in those instances in which electrolyte changes occurred any one of a number of variations was possible, but in most cases the striking changes were the reduction in the blood levels of potassium and chloride with an alkalosis and with or without elevation of the blood sodium. The alkalosis and the low blood chlorides were in no instances due to vomiting but rather were in some way associated with the disturbance of potassium metabolism. Willson and his co-workers¹¹ found, on the basis of careful metabolic studies that the reduction in plasma potassium mirrored a marked depletion of the intracellular potassium stores. These authors felt that this depletion in body potassium probably conditioned the chloride level, since the addition of potassium citrate to the diet resulted in an increase in the plasma concentration of both potassium and chlorides. On the other hand, the administration of ammonium chloride alone failed to affect the blood chloride level.

It is not surprising that patients with adrenal cortical hyperfunction should manifest alterations in the blood electrolyte levels. Anderson and Haymaker^{12, 13} demonstrated that extracts of the blood and urine of such patients were capable of prolonging the lives of adrenalectomized rats beyond the survival of untreated controls. The salt retaining effect of 1 cc. of blood was found to be equivalent to 4 to 6 grams of fresh adrenal tissue. It is astonishing, however, that such ion abnormalities are relatively infrequently observed, and it suggests the existence of some compensatory mechanism which controls the amount of salt retaining hormone manufactured under these circumstances. Some clue to the nature of this control was elicited in studies conducted in our laboratory.⁵ We observed that in normal individuals the intravenous injection of salt following the intramuscular injection of a single dose of desoxycorticosterone acetate resulted in a considerable retention of injected salt above that seen prior to the injection of the hormone. In contrast to this result, the patients with Cushing's syndrome showed a pronounced sodium chloride diuresis. The evidence would suggest that the excessive salt retaining hormone formed is rapidly converted into another substance lacking salt retaining effects. In view of the close chemical similarity between desoxycorticosterone and other adrenal steroid hormones which have no salt retaining effect, the conversion of the former into the latter would seem entirely feasible. It might be anticipated that this compensatory mechanism is not entirely effective in those individuals who manifest a disturbance in the blood electrolyte pattern. This is borne out by our observations in two cases of adrenal cortical tumors in which there was a considerable elevation of the plasma sodium. In both instances the injection of desoxycorticosterone under the conditions of our experiment failed to produce a sodium chloride diuresis.

The lack of abnormalities in the blood electrolyte pattern cannot be used as a point in differential diagnosis in adrenal cortical hyperfunction. The presence of the characteristic blood electrolyte disturbance is strongly suggestive of adrenal cortical hyperfunction. Its absence, however, does not rule out such a diagnosis.

Within recent years considerable time has been devoted to the investigation of hormonal products produced by the adrenal cortex, and attempts have been made to determine both the total amount of such compounds as well as the individual fractions in the urine of normal

TABLE II

ANDROGENIC AND ESTROGENIC COMPOUNDS
ISOLATED FROM THE ADRENAL CORTEX

Adrenosterone
11-hydroxyisoandrosterone
17-hydroxy-progesterone
Theelin

ANDROGENIC, ESTROGENIC, AND INERT COMPOUNDS
ISOLATED FROM NORMAL URINE OF MEN AND WOMEN

Androsterone
Dehydroisoandrosterone
3- α -hydroxyethicolane-17-one
Pregnanediol
Estrogens

ANDROGENIC, ESTROGENIC, AND INERT COMPOUNDS ISOLATED FROM
THE URINE OF MEN AND WOMEN WITH HYPERFUNCTION OF THE
ADRENAL CORTEX

(Tumors, Hyperplasia, Basophilism)

Androsterone
Dehydroisoandrosterone
3- α -hydroxyetiocholane-17-one
Pregnanediol
Estrogens
 $\Delta^3,5$ -androstadiene-17-one
Isoandrosterone
Pregnane-3, 17, 20-triol
3- α -hydroxyandrostene-17-one

individuals and in patients with adrenal cortical hyperfunction. Normal men and women excrete both androgenic and estrogenic compounds in the urine. These compounds, however, have their origin not only in the gonads but also in the adrenal cortices. In addition to the physiologically active compounds which are excreted in the urine and which have their origin in the adrenals, inert compounds, probably degradation products of the active substances elaborated in the adrenal cortex, are also found in the urine. Some of these compounds are present in the urines of normal men and women, while other substances exist only in pathological states associated with hyperfunction of the adrenal cortex. It is of considerable interest that the actual androgenic content of

hyperplastic or neoplastic adrenals is extremely low despite the fact that they may give rise to excessive amounts of androgenic substances in the urine. This would suggest that only minute amounts of such substances are stored in the gland where they are manufactured. In the adjoining table are listed those hormones which have been isolated and identified from the adrenal cortex, from the urine of normal men and women, and from the urine of men and women with adrenal cortical hyperfunction. Of the androgenic compounds isolated from the adrenal cortex all have androgenic activity although to varying degrees; 17-hydroxy-progesterone is about as androgenic as androsterone, while adrenosterone has an androgenic activity one-fifth of androsterone, and 11-hydroxyisoandrosterone has an androgenic activity equal to approximately one-thirtieth of androsterone. Of the androgenic compounds isolated in the urine of normals and patients with adrenal cortical hyperfunction androsterone, dehydroisoandrosterone, $\Delta_3, 5$ -androstadiene-17-one, and isoandrosterone are known to have definite androgenic activity. 3- α -hydroxyetiocholan-17-one is physiologically inert. The pregnane triols probably lack androgenic activity if one is to judge by their chemical structure. Only a limited number of androgenic and inert degradation products are found in the urine of normal men and women, while several additional compounds are excreted in the urine of patients with adrenal cortical hyperfunction. We have identified by no means all of these latter compounds, and with improvements in chemical techniques it is not unlikely that many more such compounds will be isolated and identified.

In the routine laboratory diagnosis of adrenal cortical hyperfunction it is obviously impossible to attempt to isolate the various androgenic and inert fractions from the urine. Attempts are, therefore, made to determine the total androgenic and estrogenic activity of the urine specimen without identifying individual constituents. For this purpose, androgenic activity is measured by the "capon comb growth" technique, and estrogenic activity in spayed adult rats according to the vaginal spread technique of D'Amour and Gustavson.¹⁴ In general, there is a marked variation in the urinary excretion of both androgens and estrogens, and the clinical significance of one or two twenty-four hour urine assays must not be unduly emphasized. In hyperfunction of the adrenal cortex there is a surprising lack of correlation between the clinical picture and the urinary sex hormone assays. In general it may

TABLE III

ANDROGEN AND ESTROGEN URINARY EXCRETION IN
HYPERFUNCTION OF THE ADRENAL CORTEX

<i>Diagnosis</i>	<i>Daily excretion of urinary androgens</i>	<i>Daily excretion of urinary estrogens</i>
Carcinoma of adrenal cortex	May be excessive	May be excessive
Benign tumors of adrenal cortex	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased
Hyperplasia of adrenal cortex	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased
Pituitary basophilism	Usually normal. May be slightly to moderately increased	Usually normal. May be slightly to moderately increased

be said that in carcinoma of the adrenal cortex there may be an excessive daily urinary excretion of either androgens or estrogens or both, while in benign tumors of the adrenal cortex, in hyperplasia of the adrenal cortex, and in pituitary basophilism the excretion of these urinary androgens and estrogens is frequently normal and only occasionally somewhat increased. These techniques, then, leave a good deal to be desired, both because they are rather complicated and because they yield rather meager information. It should be emphasized again that the biological determination of urinary androgens and estrogens is specific for neither one substance nor for the steroids originating from a single gland. What we are determining, in effect, are those steroids originating from the gonads and the adrenals which exercise definite androgenic or estrogenic activity. The biological assay, then, has the disadvantage of not including those steroid compounds present in the urine, and under certain circumstances in abnormal quantities, which manifest neither androgenic nor estrogenic activity. The urinary excretion of such inert compounds may be considerably increased in disease of the adrenal cortex and yet remain unidentified with the biological techniques. This may perhaps account in part at least for the infrequency with which abnormalities in assay are found to exist in patients with proven adrenal cortical disease.

TABLE IV
URINARY EXCRETION OF 17-KETOSTEROIDS IN
HYPERFUNCTION OF ADRENAL CORTEX

	<i>Number of cases</i>	<i>Normal Amount</i>	<i>Slight increase</i>	<i>increase Moderate</i>	<i>Excessive increase</i>
Virilism (no overt adrenal pathology) . . .	64	35	24	5	0
Cushing's syndrome (no overt adrenal pathology)	14	10	2	2	0
Virilism with Cushing's syndrome (adrenal cortical hyperplasia)	12	2	1	5	4
Virilism with Cushing's syndrome (adrenal cortical carcinoma) .	14	1	0	3	10

There are several advantages to the determination of the urinary 17-ketosteroids over the biological assay for androgens and estrogens. Since the determination of the urinary 17-neutral ketosteroids is a chemical procedure it is generally simpler and less time consuming than the biological assay. In addition, the urinary 17-ketosteroids include not only steroid compounds with androgenic activity but also inert compounds like 3- α -hydroxyetiocholan-17-one. However, this chemical reaction is specifically for the determination of non-phenolic neutral 17-ketosteroids and consequently testosterone, which is an androgen although not a 17-ketosteroid, is not included in the determination. Estrogenic hormone, which is a 17-ketosteroid, is not included in the determination because it is a weak phenol and is removed by the washing with alkali which is a step in the extraction process. These, then, are the disadvantages of the biochemical test for the determination of 17-ketosteroids. This method is actually not a test for androgens, although it may parallel the latter.

The normal values for the urinary excretion of 17-neutral ketosteroids vary with the age and with the sex. In general the values are lower in children than in adults, and lower in women than in men. The high value obtained in males is dependent upon the fact that these compounds are elaborated by the adrenals and by the male gonads. In our experi-

ence the twenty-four hour urinary excretion of the 17-neutral ketosteroids in women varies from approximately 5 to 15 mgm. with an average value of about 10 to 12, while in the male it varies from 8 to 18 mgm. in twenty-four hours with an average value of 15 mgm.

In Table IV are the results obtained of the urinary excretion of 17-ketosteroids in hyperfunction of the adrenal cortex. In this table it is seen that the largest excretions occur in instances of adrenal cortical carcinoma, while in patients with adrenal cortical hyperplasia there is frequently a considerable increase. In patients with virilism alone in whom there is no overt adrenal pathology, or in patients with Cushing's syndrome in whom the pathology is located mostly in the pituitary, the urinary excretion of 17-neutral ketosteroids is frequently normal and not infrequently shows only a slight to moderate increase. One cannot, therefore, draw any definite conclusions as to the diagnosis from the determination of the urinary 17-ketosteroids alone. In general, one may say that the absence of any excessive excretion is a point against, but by no means excludes, the diagnosis of an adrenal cortical carcinoma.

The diagnosis of adrenal cortical hyperfunction is therefore made on the basis of a number of factors rather than on one isolated manifestation. The factors which should be emphasized are the typical clinical history, the characteristic physical appearance, changes in the blood electrolytes, if present, and determination of the 17-neutral ketosteroids. Intravenous pyelography may help in determining the possibility of an adrenal tumor. Of even greater aid is perirenal insufflation which may show the presence of an adrenal cortical tumor or hyperplasia.

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BULLETIN OF
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SEPTEMBER 1947

TUMORS OF THE SKELETAL SYSTEM:
PATHOLOGICAL ASPECTS*

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I N the reasonable assumption that the primary tumors of bone represent the core of my subject, I shall devote my time to these. Before proceeding to the franker tumors, I wish to deal with that peculiar lesion which we have described under the name of osteoid-osteoma. Then I shall take up, in order: giant cell tumor; osteogenic sarcoma, fibrosarcoma, and chondrosarcoma; Ewing sarcoma; and multiple myeloma.

There are, of course, other primary tumors of bone, both benign and malignant. The malignant ones, in particular (such as liposarcoma, angiosarcoma and neurogenic sarcoma), are very rare, and we shall make no further mention of them. With certain of the benign tumors, we shall deal at least in passing, pointing out, for instance, that an enchondroma or an osteochondroma may be the point of departure for a chondrosarcoma. The benign tumors of bone also include hemangioma and neurofibroma. Furthermore, they include a number of other

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lesions which (because they may contain some giant cells), have, in the past, been loosely classed with giant-cell tumor of bone—usually as some form of giant-cell tumor variant. Time does not permit any discussion of the pathology of these various benign tumors of bone. In particular, we shall not be able to consider the pathology of those which, in the past, have been uncritically linked with giant-cell tumor. Time likewise does not permit consideration of the primary tumors of the periosteum per se (which, incidentally, are quite rare), nor of tumors of articular capsules. Also, it does not allow us to consider the many interesting pathologico-anatomic questions relating to tumors metastatic to bone.

OSTEOID-OSTEOMA

An osteoid-osteoma¹ is a very peculiar, small, benign, tumorous lesion developing as a nidus in a bone. When well advanced in its evolution, the lesion consists, in varying proportions, of osteoid and trabeculae of newly formed osseous tissue, set in a substratum of highly vascularized osteogenic connective tissue.

The lesion is by no means rare. It predilects adolescents and young adults. The site of the lesion is found to be a tibia or a femur in about half of the cases, and any one of a number of other bones in the other half. The speaker has not yet observed it in a rib or in the calvarium. In a given affected bone, the lesion may lie within the spongiosa, or against the inner surface of the cortex, or even within the cortex. Though the osteoid-osteoma does not usually exceed a centimeter in its greatest diameter, the total abnormal area in the affected bone may be found considerably extended by a perifocal zone of bone thickening or sclerosis.

The diagnosis of osteoid-osteoma is not very difficult if one is familiar with its clinical peculiarities and if it has advanced sufficiently in its evolution to be demonstrable roentgenographically. Anatomically, if an osteoid-osteoma is removed intact from its setting, or at least removed without being crumbled, it stands out strikingly, especially in the tissue sections. Its complete benignity is attested by the fact that, in no case in which the lesion has been completely removed surgically has there ever been a recurrence, and when it has been removed the complaints (mainly of local pain) cease with dramatic promptness.

GIANT-CELL TUMOR

As has already been indicated, the term "giant-cell tumor of bone" had long been loosely applied, having been used not only for giant-cell tumor proper, but likewise for a number of other lesions, usually with the qualification "variant." In a systematic study of the question, we² have shown that there is no firm pathologic basis for such designations as the "calcifying or chondromatous variant" of giant-cell tumor, the "spindle-cell variant," the "xanthic variant," or the "cystic variant." We have stressed the idea that these so-called "variants" have little in common, clinically and anatomically, with genuine giant-cell tumor, and also little in common with each other except an auspicious prognosis. When, as is increasingly being done, one segregates these so-called "variants" away from the real giant-cell tumor, the latter comes to stand out all the more. One finds it to be a relatively uncommon, highly distinctive tumor, which, far from being consistently benign, often comes to show aggressive qualities.³

The age incidence of giant-cell tumor is worth remarking. It is rarely observed in a person under 20 years of age. As to localization, the lesion strongly predilects the ends of long bones. When situated in a long bone, it is usually found implicating some part of an epiphyseal end of the bone and the adjacent metaphysis. The presence of more than one giant-cell tumor of bone in the same person (that is, the appearance of this tumor otherwise than as a solitary lesion) is very rare indeed, but the speaker has seen an anatomically proved instance of this.

Especially if not modified by previous treatment, a transected giant-cell tumor intact in its setting (for instance in the end of a long bone) is not likely to be confused with anything else. Furthermore, on the roentgenographic side, it is only rarely that a giant-cell tumor (in a long bone, for instance) shows anything like the multilocular, cyst-like "soap-bubble" appearance which is frequently maintained to be "typical" for it.

Like the gross, the histologic picture of giant-cell tumor is clearly characterized. The viable and otherwise unmodified tumor tissue is composed essentially of a vascularized network of spindle-shaped or ovoid stromal cells, heavily interspersed with multinuclear giant cells. Mainly on the basis of differences in stromal-cell detail, one can grade

the giant-cell tumors in respect to their aggressiveness. Aggressiveness is attested by increase and crowding of the stromal cells, plumping up of these cells, and particularly of their nuclei, the presence of many stromal cells undergoing mitotic division, and the presence of stromal cells with one or more very large nuclei. Along these lines, we sub-classify giant-cell tumor into three grades—I, II, and III—showing respectively, no appreciable, moderate, and pronounced atypism of the stromal cells. The giant-cell tumors of grade III present a sarcomatous stroma and are already frankly malignant. Occasionally a malignant giant-cell tumor is already so (that is, a tumor of grade III) when studied for the first time anatomically. Usually, however, grade III represents malignant transformation, through successive recurrences, of a tumor which when first studied, was of grade I or II. The prognosis in cases of giant-cell tumor is very bad, because of its strong tendency to metastasize. Indeed, very often the tumors of grade II already show such local clinical aggressiveness that the affected limb has to be amputated.

OSTEOGENIC SARCOMA, FIBROSARCOMA, AND CHONDROSARCOMA

In its revised (1939) classification, the Registry of Bone Sarcoma⁴ gives recognition to chondrosarcoma as a tumor entity distinct from osteogenic sarcoma, but still does not recognize the entity of fibrosarcoma of bone. Whether one does recognize fibrosarcoma of bone as an entity depends upon the histogenetic definition which one accepts for osteogenic sarcoma. The Registry defines the latter as a sarcoma derived from the tissue presumably intended to form bone, irrespective of whether it eventually does so. By this definition, fibrosarcoma can logically remain a sub-form of osteogenic sarcoma of bone. On the other hand, in the case of a sarcomatous connective-tissue tumor of bone which fails to express any bone-forming capacity whatever in the course of its full evolution, what evidence is there that the tumor in question has arisen from "osteogenic" and not from neutral or supporting connective tissue? On a strict oncologic basis, it would seem appropriate to designate such a tumor as a fibrosarcoma of bone, and we do.

OSTEOGENIC SARCOMA

It is only as a primary malignant tumor appearing *de novo* in a bone that osteogenic sarcoma concerns us here. That is, we shall not

consider it in connection with its occurrence as a common complication of Paget's disease of bone, nor are we concerned with extra-skeletal osteogenic sarcoma.

Even apart from its occurrence as a complicating tumor, osteogenic sarcoma is the most common of the malignant tumors of bone. As an independent primary bone tumor, it strongly predilects the age group between 10 and 25 years. It is a tumor with an extremely high mortality rate, no matter how the case is treated. The five-year survival rate in our experience is definitely less than 10 per cent. It is to be suspected that recorded survival rates of 20 or 30 per cent or even more reflect an inclusion, in the reported material, of lesions other than osteogenic sarcoma, and specifically cases of chondrosarcoma, cases of fibrous dysplasia in a single bone, cases representing relatively benign fibrous or osseous proliferations of the periosteum alone, etc.

Osteogenic sarcoma develops most commonly in long bones. In a long bone, the tumor usually involves one end of the shaft and at least part of the adjacent epiphysial area, though sometimes it is situated well toward the middle of the shaft.

Contrary to the statement often made that the tumor takes its departure from periosteum, the fact seems rather to be that it begins its growth in the interior of the affected bone area. However, most osteogenic sarcomas, when first seen, not only involve the interior but have somewhere already penetrated the cortex, to lie beneath the periosteum, or have even perforated the latter in some places and gone on growing beyond it. Irrespective of whether the lesion is still largely confined within the limits of the bone or already lies to a considerable extent beyond these limits, an individual tumor may show relatively little, moderate, or very considerable ossification.

In our series of osteogenic sarcoma, about one quarter were relatively ossified, about one quarter moderately ossified, and one half heavily ossified and considerably eburnated. On the whole, the less ossified the tumor, the more likely it is to show considerable necrosis, cystification, and telangiectasis as secondary features of its pathologic anatomy, though even highly ossified tumors occasionally show considerable telangiectasis, particularly in their more peripheral portions. Prognostic significance has sometimes been attached to the intensity of ossification shown by an individual tumor, but the fact is that, as a rule, the disease reaches its fatal termination about as quickly when

the original tumor is a highly ossified one as when it is not.

Metastasis seems to occur mainly, if not exclusively, by the hematogenous route. Spread of the tumor from the original bone site to the regional lymph nodes seems to be of rare occurrence. Pulmonary metastases are consistently present in the cases which terminate fatally, and death commonly supervenes within two years (and often within a matter of months) from the time when the patient first comes under treatment.

On the whole, osteogenic sarcoma is a lesion relatively easy to diagnose on the basis of the x-ray picture. Difficulties are created largely by those cases in which ossification is slight and the x-ray picture therefore ambiguous. On the other hand, when radiopacity is moderate (that is, fairly well developed, though not dominating the lesional shadow as a whole) a diagnosis of osteogenic sarcoma can already be made with reasonable confidence from the x-ray picture. In regard to the highly ossified and eburnated tumors (that is, frank, sclerosing osteogenic sarcoma) the pre-operative diagnosis on the basis of the x-ray picture becomes even more certain. However, in studying and evaluating the roentgenographic picture in any particular case, even if the lesion shows moderate or intense radiopacity, one must, of course, consider this picture within the framework of the case as a whole. Thus, except in rare instances, if the patient is a child or at most a young adult, the lesion is a solitary one lying toward one end of a long bone, and the shadow it casts is strikingly radiopaque, the lesion is found, on anatomic examination, to be an osteogenic sarcoma. On the other hand, even if the lesion is oriented toward the end of a long bone and casts a strikingly radiopaque shadow and Paget's disease has been ruled out, if the patient is a mature or older adult, the reservation that one may be dealing with some other lesion (for instance an osteoplastic carcinoma metastasis) has to be explored.

Time does not permit more than a few general remarks about the histologic findings in osteogenic sarcoma. In a given lesion, the still unmodified stromal tissue may be composed predominantly of spindle-shaped cells or may be definitely anaplastic and present a highly polymorphous cellular character. Its osteoid and osseous transformation is prepared by collagenization, which spreads irregularly through it. Scattered and focal deposition of calcium in the collagenized stroma then inaugurates the appearance of actual tumor bone. Interestingly enough,

the stromal tumor cells which have become incarcerated in intercellular matrix look less ominous histologically than the cells of the neighboring still uncollagenized and unossified sarcomatous stroma. If the tumor is one whose sarcomatous stroma does not lay down much tumor osteoid and bone, the original osseous tissue (both spongy and cortical) at the site of its growth is subjected from the beginning mainly to resorption and dissolution. If the lesion is one whose sarcomatous stroma does lay down much tumor osteoid and bone, the highly sclerotic and eburnated areas in the interior of the affected bone part are found to result from superposition of ossified tumor tissue upon the preëxisting spongy trabeculae, with consequent obliteration of the spongy marrow spaces. The presence of densely ossified areas of tumor tissue outside of the cortex, especially in these cases, can be shown to be due to the intermingling of actively ossifying tumor tissue with reactive non-tumorous new bone of periosteal origin.

FIBROSARCOMA

As noted, we mean by fibrosarcoma of bone a primary connective-tissue sarcoma of bone which does not demonstrate any osteogenic potentialities, either in its local growth or in its metastases. In its anaplastic form, the lesion has a very ominous prognosis, but the more differentiated fibrosarcomas are of lesser malignancy. Its most common site is a long bone of an extremity, where it usually starts its development in the interior of a shaft end. In such a bone, the tumor tissue fills the spongy marrow spaces at the site of its growth and induces more or less lytic destruction of the spongy trabeculae which it encircles. It gains exit by penetrating through the cortex over at least part of the circumference, and finally produces an overlying tumor mass of smaller or larger proportions.

The roentgenographic reflections of these changes are often difficult to interpret, on account of their ambiguity. Thus, if the lytic resorption of the spongy bone is not pronounced, the interior of the affected bone area may present merely vague vacuolation. Though it may be plain that the cortex has been broken through in places, the overlying tumor mass, totally lacking osseous tissue, is sometimes difficult to visualize unless soft-tissue technique has been employed. Even when it is clear from the x-ray picture as a whole that one is dealing with a malignant tumor, biopsy is required to delimit its character.

The biopsy specimen will show a connective-tissue sarcoma whose stromal cells may be predominantly spindle-shaped or, on the other hand, rather polymorphous, but in either case fails, of course, to show tumor osteoid and bone developing in the stroma. It is clear that from such an examination alone one cannot be sure that one is dealing with a fibrosarcoma and not with a still-unossified area of an osteogenic sarcoma. If one is to be sure, ample sampling of the amputation specimen must have shown beyond a reasonable doubt that the tissue is non-osteogenic throughout. In such cases, furthermore, the metastases, too, will prove to be non-osteogenic, thus sustaining the interpretation of the original lesion as a fibrosarcoma.

CHONDROSARCOMA

As a malignant tumor arising from already preformed cartilage, chondrosarcoma⁵ stands apart histogenetically from osteogenic sarcoma and fibrosarcoma of bone. Indeed, in regard to a given chondrosarcoma, it is often possible to show or deduce from the roentgenographic and pathologic findings that it has arisen from an originally benign cartilage growth, and specifically from an enchondroma (in a case of solitary or multiple enchondroma of bone) or the cartilage cap of an osteochondroma (in a case of solitary or multiple osteocartilaginous exostosis).

The incidence of chondrosarcoma of bone is somewhat less than half of that of osteogenic sarcoma. The patients are usually between 25 and 50 years of age, and only occasionally are they still in their teens. Long bones, innominate bones, and ribs, in descending order of frequency, seem to be the most common sites for development of the lesion.

For gross anatomic orientation, a chondrosarcoma which begins its development in the interior of a bone is often denoted as a central chondrosarcoma, and one which begins in the cartilage cap of an exostosis as a peripheral chondrosarcoma. A central chondrosarcoma usually gains exit from the bone slowly, and where it is penetrating the cortex, the latter may even thicken. After issuing from the bone, the proliferating tumor tissue invades the overlying soft parts, producing larger or smaller tumor masses attached to the bone. The tumor cartilage in the interior of the bone may or may not have focal areas of calcification and ossification, but the tumor cartilage around the bone is strikingly lacking in these respects. In particular, where the tumor

tissue outside of the cortex is unmodified (by hemorrhage, mucoid degeneration, or cystification) it is composed of smaller or larger facets of glistening white cartilage.

As to peripheral chondrosarcoma, it is interesting that, even when reaching a large size, the tumor tends to retain some sort of cartilage cap, however exuberant and irregular in outline, thus still suggesting in its outward appearance, though in a distorted way, an osteocartilaginous exostosis. Its cap is demarcated in places by an endochondral ossification line from the deeper portion of the growth, which is composed of islands of cartilage and is always heavily interspersed with foci of calcification and ossification.

It is sometimes a matter of years before a cartilage growth which is undergoing malignant transformation has reached a stage in which the cytologic picture of the tumor expresses obvious full-fledged malignity. This is manifested in pronounced cellularity of the tumor tissue, and a general plumping of the nuclei of the cartilage cells. Also, many of the cartilage cells, though still relatively small, are binuclear, while many giant cartilage cells with large, bizarre single and multiple nuclei are also to be seen. Before this stage is reached, the lesion is likely to be "underdiagnosed" by the pathologist if he does not appreciate the significance of subtle evidence of atypism of the cartilage cells, tending in this general direction and already discoverable, at least in some fields, in the lesional tissue submitted to him.

Clinically, even after the tumor has reached full-fledged malignity, it often still remains locally invasive for a long time, although exceptionally a case may run a fulminating course. All this makes it clear why, in general, chondrosarcoma is a tumor so much less immediate in its threat to life than osteogenic sarcoma or fibrosarcoma of bone. In fact, if the lesion is in a site accessible to surgical intervention and the latter is not "too little and too late," a fairly good prognosis can be offered for the case in question.

When breaking its local bounds, whether sooner or later, the tumor spreads by irrupting into the regional venous channels and continues its growth in the major veins draining the part, without necessarily adhering very much to the vessel walls. Eventually it may extend to the heart and lungs in cord-like plugs, but often no parenchymal metastases are found at autopsy. In other cases, it does give rise to parenchymal metastases, at least in the lungs, though rarely to other organs.

EWING SARCOMA

Contrary to the belief held in some quarters, our experience supports the idea that a primary bone tumor entity corresponding to what Ewing attempted to single out does exist.⁶ The tumor is not a particularly common one, and the patients are mainly in the age group between 10 and 25 years. The presenting lesion (that is, the one causing the complaints which lead the patient to seek medical care) is most commonly in a long bone or one of the bones of the trunk—very often an innominate bone. The idea that the presenting bone lesion shows a characteristic, if not typical, roentgenographic picture of high diagnostic value does not stand up under close scrutiny.

At the time when the presenting lesion is first identified as a Ewing sarcoma, x-ray examination of the entire skeleton usually fails to reveal evidence of tumor in the other bones. Even under these circumstances, however, there is no doubt that in some cases the marrow spaces of many of the bones already contain tumor tissue. Clinically, in a given case, persistent mild fever, secondary anemia and an increased sedimentation rate of the blood can be taken as evidence of this, whether or not sufficient lytic destruction of spongy bone and cortex has taken place to show up in the x-ray films. As autopsy discloses, the evolution of the disease is regularly associated with widespread involvement of the skeleton, practically all the bones eventually becoming riddled through with tumor tissue. Even just before death, however, the x-ray findings hardly reflect the severity of the actual involvement. Of the internal organs, the lungs bear the brunt of the metastases. Altogether, Ewing sarcoma is a disease having a most doleful prognosis, it being doubtful whether there is more than an occasional instance of survival in an unequivocal case.

Beyond the fact that it is a specific malignant tumor primary in bones, there is still much to be learned about Ewing sarcoma in respect to its histogenesis. We incline toward Oberling's idea that the tumor cells of the Ewing sarcoma are derived from the supporting framework (the reticular tissue) of the bone marrow—a framework which can be regarded as a mesenchymal or primitive form of connective tissue. This idea does not support Ewing's own contention that the tumor cells are derived from capillary or vascular (or perivascular) endothelium.

In well-preserved tumor tissue, the cells appear in a sort of net-

work, lack delimiting membranes, are connected by short or long cytoplasmic processes, and have a fairly large, round or oval nucleus showing scattered chromatin. The often stressed perivascular orientation (so-called perithelial arrangement) of the tumor cells is likewise not a characteristic cytologic feature of the tumor, although it may be observed in tumor areas which have become heavily invaded by blood vessels, especially in the wake of hemorrhage. Furthermore, the formations suggestive of rosettes have been overstressed as part of the cytologic picture. When, in an occasional lesion, one finds formations in which cells show ring-like arrangements (though not around a vessel) these formations can be seen to have resulted from degeneration of centrally located cells whose shadows are still perceptible.

Finally, it is necessary to stress the idea that diagnosis of Ewing sarcoma from a biopsy specimen, even if the latter is obtained by surgical incision, has to be made with great circumspection, because of the numerous possibilities for error. If one observes proper caution, the diagnosis of Ewing sarcoma will not be pronounced too often, but will be made with a discrimination which will help to do away with the disappointment of not having autopsy confirm the diagnosis made on the basis of biopsy findings.

MULTIPLE MYELOMA

Unfortunately, time permits only a few general remarks about multiple myeloma. This is a distinctive primary cancer apparently taking its departure from the myeloid-formative tissue proper. Anatomically, practically every bone may ultimately come to be involved, more or less, in a given case. Progress of the disease over the skeleton may be steady and rapid, sometimes from the beginning and sometimes after a static period. One gathers also that in some cases, before the disease becomes spread over the skeleton, it may flourish in one bone (as a so-called solitary myeloma) for months or even years. It is only seldom that the disease shows any metastatic spread whatever to the viscera or lymph nodes.

It is associated, however, with almost pathognomonic cytologic changes in the kidneys. Specifically, the latter almost constantly show plugs of proteinaceous material (often surrounded by foreign-body giant cells) in the renal tubules in the cases coming to autopsy. The plugging tends to lead to tubular atrophy and also to interstitial scar-

ring, and, if widespread, to renal insufficiency, sometimes very severe. In cases in which such renal changes are found at autopsy, the patient may or may not have shown Bence-Jones proteinuria and hyperproteinemia during life. The kidneys, and specifically the tubular epithelium and interstitial connective tissue, often also show deposits of calcium granules, and in some cases the metastatic calcifications may be quite heavy and widespread, involving, in addition, the interstitium of the lungs, the lining of the stomach, and even other tissues. This is not at all surprising in view of the relative frequency of hypercalcemia⁷ (connected with the lytic resorption of the bones) and the tendency toward renal failure in many of the cases.

Another arresting feature of the pathologic anatomy of multiple myeloma is the presence of amyloid in some cases. So far as the skeleton is concerned, if amyloid is found, it usually presents as scattered deposits detectable only microscopically in the neoplastic tissue of the affected bones. In an occasional case, however, one may find not only the microscopic deposits, but large agglomerations of amyloid, substantially replacing large myelomatous tumor foci. On the other hand, we observed a case of so-called atypical amyloidosis with myeloma in which autopsy failed to reveal evidence of amyloid in the myelomatous tissue itself, though practically all the extra-skeletal tissues and organs, including the voluntary muscles, were heavily infiltrated with amyloid.

It would be futile to attempt to do justice here to the gross appearance of the bones as one notes it in one case or another of multiple myeloma coming to autopsy. It does seem worth while to point out, however, how often one finds multiple myeloma presenting itself clinically because an exuberant focus of the disease has developed in a vertebral body (or several contiguous bodies). In these cases indeed the tumor tends to transgress them, often producing pressure on the cord or local nerve trunks, with the resultant symptoms. In such cases, roentgenographic examination of the rest of the skeleton (including the skull) often fails to reveal the clear-cut punched-out rarefactions which are conventionally held to distinguish the roentgenographic picture of multiple myeloma. It is in such cases (especially if one dorsal or lumbar body alone is clearly affected) that the true nature of the disease often goes unrecognized for long periods, the lesion frequently being interpreted as a local one such as a hemangioma, giant-cell tumor, or Kümme's-disease fracture, or, if grossly destructive, as a focus of meta-

static malignancy. The true nature of the disease in these cases may become clear if a sternal marrow puncture is done, or when serial x-rays of the rest of the skeleton finally demonstrate widespread lesions in other bones suggesting multiple myeloma, but sometimes it is discovered only at autopsy.

A somewhat special interest attaches to the calvarium. Great emphasis is usually laid upon the diagnostic value of several or even many roundish punched-out rarefactions in x-ray films of the skeleton. It is true that when x-rays show clear-cut and widespread involvement of the rest of the skeleton, in the form of numerous punched-out rarefactions, the calvarium, too, is quite likely to show these, though not infrequently it does not. However, precisely when one turns to the films of the calvarium because the films of the other bones do not show the conventional picture of multiple myeloma, the calvarium too fails to show it. Whether or not the calvarium shows rarefactions in the films, histologic examination will reveal that the marrow of the diploic spaces has been substantially replaced by the tumor tissue. At sites of clear cut rarefactions, one will find that the tumor tissue is present as a nodule which has encroached upon and destroyed the diploic bone, sometimes also thinning the tables, but, in our experience, the tables are seldom perforated, even in such sites.

As to the cytology of the tumor cells proper, it has been recognized and must be emphasized that the cytologic picture is not the same in all cases of multiple myeloma. Roughly, however, they can be fitted into two general cytologic groups. On the one hand, there are the cases in which the tumor cells are predominantly small and bear a superficial resemblance to plasma cells. In these cases, they are roundish and have a stippled nucleus substantially filling the cell. Interspersed among them may be some cells which, though of the same general character, are larger in respect to both cytoplasm and nucleus. It is to the myelomas showing this cytology that the name "plasma cell myeloma" or "plasmacytoma" is commonly applied.

In the other group of myelomas, the cytologic picture tends to be dominated by cells larger than those resembling plasma cells but may be a rather variegated one. The dominant cells in the tumors of this group generally exceed the myeloblast in size and, on the whole, show fairly abundant cytoplasm and have a large, round, oval, or even reniform, pale, stippled nucleus. However, in any particular tumor site

examined, one may also find some of the smaller cells resembling plasma cells, or, on the other hand, find cells which are much larger than the dominant ones and usually show nuclear atypism. Specifically, such atypical cells may present large and hyperchromatic nuclei, giant nuclei of bizarre shape, or two or more nuclei.

SUMMARY

This presentation of the pathologic aspects of tumors of the skeletal system deals only with the primary tumors, and specifically only with: osteoid-osteoma; giant-cell tumor; osteogenic sarcoma, fibrosarcoma, and chondrosarcoma; Ewing sarcoma; and multiple myeloma. Even as to these, only the minimum essentials of the pathology could be given, but, as much as possible, this was correlated in a practical way with the x-ray picture and the clinical course of the condition.

The high-light of osteoid-osteoma is the surprising amount of pain and disability caused by this small lesion, and the promptness and permanence of the relief when it is completely excised.

As to giant-cell tumor, we stressed the fact that when one segregates from it the so-called giant-cell tumor variants, the tumor is found to be one which should not be taken lightly, since it often comes to show aggressive qualities.

In regard to osteogenic sarcoma, emphasis was laid on the definition of this as a connective-tissue sarcoma of bone in which the stroma actually forms some osteoid and osseous tissue in the course of the tumor's evolution. On this basis, fibrosarcoma of bone—a primary connective-tissue sarcoma which does not demonstrate any osteogenic potentialities either in its local growth or its metastases—is regarded by us as an independent entity, and not as a sub-form of osteogenic sarcoma.

It was pointed out that chondrosarcoma stands apart histogenetically from osteogenic sarcoma and fibrosarcoma, since it arises from already preformed cartilage, that it is slow in reaching full-fledged malignity, and that, if accessible to surgical intervention, it has a much more auspicious prognosis than either osteogenic sarcoma or fibrosarcoma of bone.

As to Ewing's sarcoma, we incline toward Oberling's idea that the tumor cells are derived from the supporting framework (the reticular tissue) of the bone marrow—a framework which can be regarded as a mesenchymal or primitive form of connective tissue. It was also brought out that in well-preserved Ewing tumor tissue the cells appear in a

sort of network, lack delimiting membranes, are connected by short or long cytoplasmic processes, and have a fairly large, round or oval nucleus showing scattered chromatin, and that, on the other hand, "perithelial arrangement" and "rosette arrangement" of the tumor cells are fortuitous and have been overstressed.

Finally, in regard to multiple myeloma, it was pointed out that often this presents itself clinically because an exuberant focus of the disease has developed in a vertebral body (or several contiguous bodies) and that in such cases roentgenographic examination of the rest of the skeleton (including the skull) often fails to reveal the clear-cut punched-out rarefactions which are conventionally held to distinguish the roentgenographic picture of multiple myeloma.

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* This article deals with the lesions which have sometimes been called "giant-cell variant of bone cyst or osteitis fibrosa", "healing variant of giant-cell tumor", "xanthic variant of giant-cell tumor", etc.

TUMORS OF THE SKELETAL SYSTEM: MEDICAL ASPECTS*

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ALL too often the internist or general practitioner is apt to feel that the problems presented by tumors of the skeletal system do not come within his province and should be relegated to one or another specialty. This attitude may have unfortunate consequences. It is usually the family doctor or the physician concerned principally with internal disease whom the patient with early manifestations of bone tumor first consults. The awareness of the physician and the promptness with which he institutes the measures necessary for the diagnosis and treatment may be deciding factors in determining the subsequent fate of his patient.

This special responsibility arises from the circumstance that the first indication of bone tumor, whether malignant or benign, primary or secondary, is apt to be pain. Usually the pain is localized to the site or sites of skeletal involvement, and it may be possible to elicit tenderness on pressure over the involved bone. In more generalized types of skeletal involvement, however, particularly in the older age groups, the initial complaints may be diffuse and confused with "rheumatism" or "old age." In the case of vertebral involvement and root pain, the complaint may be referred to the corresponding distant area; sciatic distribution of pain, so often misdiagnosed, is a classic example. As a rule, movement of the affected part, or weight-bearing, causes exacerbation of pain which the patient recognizes as deep and not superficial and often as originating in the bony structure. Restriction of mobility and splinting, if already present, help to localize the lesion. Inspection and palpation may reveal a swelling recognizable as of bone because of its location, hardness and immobility. Palpation may also elicit a parchment-like crackling, particularly in central giant-cell tumors and bone cysts. The pain may be indicative of a fracture, so often not preceded

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by overt trauma, and frequently the first indication of skeletal involvement.

While pain often is the initial symptom of bone tumors, the onset may be painless and insidious, characterized by anemia, weight loss, fever and other systemic symptoms which may present great difficulty in diagnosis.

The differential diagnosis of bone tumors necessitates careful history-taking and physical examination, roentgenographic study with expert interpretation, chemical studies of the blood and often final recourse to biopsy. I should like to devote the major part of the time allotted me to a discussion of the role of chemical studies of the blood since these represent a comparatively recent development, with potentialities which frequently are not fully exploited even when the necessary laboratory facilities are available. The discussion will be confined largely to a consideration of the indications for and rationale of the relevant estimations, and to the principles and mechanisms involved. I shall not attempt any systematic classification of bone disease on the basis of chemical findings in the blood.

The blood constituents of principal importance in the differential diagnosis of bone disease are calcium and inorganic phosphate, the major mineral components of bone; the enzymes alkaline phosphatase and acid phosphatase; and the serum proteins. The normal range of these components, together with the general significance of increased or decreased serum levels, are indicated in Table I.

The normal range of serum calcium is generally stated to be 9 to 11 mg. per cent, though the variation actually observed in most normal individuals is within more narrow limits, about 10.2 to 10.9 mg. per cent, and is maintained within these limits with remarkable constancy. In most cases of bone tumor the serum calcium level is not disturbed significantly. The disorders in which definite hypercalcemia occur are few in number, all associated with such rapid, widespread dissolution of bone that calcium salts are poured into the bloodstream even faster than they can be excreted or deposited. In fact, the finding of marked hypercalcemia is so uncommon as to have definite diagnostic value, usually indicative of hyperparathyroidism, hypervitaminosis D, multiple myeloma or osteolytic bone metastases. In multiple myeloma, hypercalcemia occurred in one-third to one-half of the cases in the literature and, as seems clear now, is not related to the serum globulin or Bence-

TABLE I

BLOOD CONSTITUENTS IMPORTANT IN THE DIFFERENTIAL DIAGNOSIS OF BONE DISEASES

	<i>Normal range</i>	<i>Significance of increased blood levels</i>	<i>Significance of decreased blood levels</i>
Calcium	9-11 mg. %	Rapid, wide-spread mobilization of bone salts (hyperparathyroidism, osteolytic bone metastases, multiple myeloma, hypervitaminosis D).	Hypoparathyroidism; impaired absorption of calcium from the gastrointestinal tract; increased demands in pregnancy and lactation.
Phosphate, inorganic	2.8-4 mg. %	Renal insufficiency; secondary hyperparathyroidism; hypoparathyroidism; multiple myeloma; obstructing tumors of the genitourinary tract with bone metastases.	Vitamin D deficiency (rickets, osteomalacia); hyperparathyroidism; sprue; impaired reabsorption by renal tubules.
Phosphatase, alkaline	1.5-4.0 Bodansky units %	Markedly increased osteoblastic activity (Paget's disease, rickets, hyperparathyroidism, osteogenic sarcoma, osteoplastic bone metastases); biliary tract obstruction (obstructive jaundice, liver metastases).	
Phosphatase, acid	1-3 units %	Metastasizing prostatic carcinoma	
Serum proteins	Total proteins: 6-8 gm. % Globulins: 1.5-2.5 gm. % Bence-Jones protein: 0	Certain chronic infections (lymphogranuloma venereum, kala-azar, sarcoid, etc.); hepatic cirrhosis; multiple myeloma.	Serum albumin decreased in malnutrition, nephrosis, cirrhosis

TABLE II—CASE S.H., AGE 73

METASTASIZING PROSTATIC CARCINOMA (PROSTATECTOMY APRIL 1937)

<i>Date</i>	<i>Serum acid phosphatase</i> (units/100 cc.)	<i>X-ray findings</i>	<i>Clinical comment</i>
April 1938	5.6	Osteoplastic metastases to pelvis and spine	Bone pain
Feb. 1939	14.4	Further spread of metastases	Radiotherapy
May 1939	13.5		
Dec. 1939	31.3	Further spread of metastases	
July 1940			Died

Jones protein content of the blood, but to the extent and rapidity of bone destruction. Hypercalcemia is found in association with metastatic skeletal involvement only when there are extensive bone metastases that are osteolytic in character and rapidly progressive. Carcinoma of the breast, bronchogenic carcinoma and hypernephroma are the most common primary tumors giving rise to osteolytic bone metastases and the finding of hypercalcemia may be helpful in establishing the presence of these tumors.

The normal inorganic phosphate content of serum, expressed as phosphorus, varies from about 2.8 to 4 mg. per cent in the adult. The significance of elevated and depressed levels is indicated in Table I. The determination is helpful in the differential diagnosis of bone tumors chiefly in the recognition of hyperparathyroidism, in which serum phosphate is low so long as there is no significant renal damage with phosphate retention. Multiple myeloma is one of the few tumors destructive of bone in which there may be accompanying damage to both kidneys, with phosphate retention in the blood; this is due to obstruction of tubules by the precipitation out of Bence-Jones protein or other abnormal proteins in the urine undergoing concentration by reabsorption of water in the tubules. Prostatic carcinoma metastasizing to the bones may also cause hyperphosphatemia through obstruction of the bladder neck by growth of the primary tumor.

The alkaline phosphatase activity of normal blood serum in the adult varies from about 1.5 to 4 Bodansky units per 100 cc. So far as known, most of this enzyme is derived from bone-forming cells in bone and calcifying cartilage. The enzyme appears to function at the surface of these cells and is then excreted, being transported by the lymph into the bloodstream, passing through the liver into the bile. There are two general conditions in which the alkaline phosphatase activity of the blood is significantly increased: (1) when there is markedly increased osteoblastic activity leading to increased formation of the enzyme; (2) when the biliary tract is obstructed so that the excretory pathways through the liver are blocked and retention of the enzyme in the bloodstream results. The primary bone tumor most likely to cause increased alkaline phosphatase activity of the serum is osteogenic sarcoma and determination of the enzyme is helpful both in the diagnosis of osteogenic sarcoma and in following the results of treatment. Increased values are observed also in association with osteo-

TABLE III
EFFECT OF CASTRATION ON SERUM ACID AND ALKALINE
PHOSPHATASES IN TWO PATIENTS WITH METASTATIC
PROSTATE CARCINOMA

(Case T.B. Did Well Clinically, Case L.B. Died in 5 Months)

	<i>Case T. B.</i>		<i>Case L. B.</i>	
	<i>Acid Phos- phatase, Units per 100 cc.</i>	<i>Alkaline Phos- phatase, Bodansky Units per 100 cc.</i>	<i>Acid Phos- phatase, Units per 100 cc.</i>	<i>Alkaline Phos- phatase, Bodansky Units per 100 cc.</i>
Preoperative	80.6	43.3	44.8	12.4
Postoperative				
2 days	68.6	31.6	45.8	9.8
5 days	42.2	31.1	37.0	12.1
1 week	21.1	38.3	35.0	15.1
2 weeks	39.3	17.3
3 weeks	7.4	52.1	42.5	15.2
4 weeks	35.7	12.0
8 weeks	3.0	23.7	59.0	10.2
12 weeks	4.1	13.4	393.0	23.6
16 weeks	3.6	8.3	740.0	33.9

TABLE IV
RESULTS OF CASTRATION FOR METASTASIZING PROSTATIC CARCINOMA
IN 56 CASES FOLLOWED 6 MONTHS TO 2 YEARS

	<i>After 6 months</i>	<i>After 1 year</i>	<i>After 1-1/2 yrs.</i>	<i>After 2 years</i>
Total no. cases	56	40	25	14
Lost to follow-up	3	2	2	1
Available for analysis	53	38	23	13
1. Died	6*	8	3	2**
2. Surviving	47	30	20	11
a. markedly improved	38	23	15	5
b. moderately improved	6	4	4	2
c. not improved	4	3	1	4

* 1 death due to myocardial infarction, another to perforated peptic ulcer.

** 1 death due to myocardial infarction.

plastic metastases to the bones, most commonly secondary to prostatic carcinoma. Metastatic involvement of the liver is also frequently associated with some increase in serum alkaline phosphatase activity and the determination sometimes is helpful in the early detection of spread of cancer to the liver.

The acid phosphatase activity of normal blood serum varies from 1 to 3 or 4 units per 100 cc., as determined by an adaptation of the King and Armstrong method we have proposed. Increased values are found in approximately 85 per cent of patients with metastasizing prostatic carcinoma, the blood level usually rising as the tumor spreads (Table II).

The determination of serum acid phosphatase has proven consistent and specific enough to be helpful in the following clinical applications:

1. Corroboration of the clinical diagnosis of metastasizing prostatic carcinoma.
2. Indicating spread of prostatic carcinoma before this may be demonstrable by x-ray.
3. Determining prostatic or non-prostatic origin of tumor in patients known to have metastases.
4. Differentiating Paget's disease from metastatic prostatic carcinoma.
5. Selection of cases for radical prostatectomy.
6. Follow-up of the results of castration and of treatment with estrogens.

The use of the determination in following the patient's course after castration is indicated in Table III where Case T.B. illustrates the findings when amelioration of symptoms is prolonged, Case L.B. when castration is followed by no symptomatic improvement. Table IV summarizes the clinical results of castration in 56 patients followed at the Presbyterian Hospital over a period of two years.

The determination of serum proteins is often helpful in the diagnosis of multiple myeloma since over half of the cases reported in the literature show hyperproteinemia. The increase may involve both the euglobulin fraction and the pseudoglobulin fraction (as determined by Howe's method) and may thus be indistinguishable from that observed in certain chronic infectious diseases except that the total protein level may be so high as to exclude most of them. In some instances of multiple myeloma peculiarities in the salting-out behavior of the proteins, due to the presence of Bence-Jones proteins and other ab-

normal proteins, may be noted and these are virtually pathognomonic. Marked hyperglobulinemia without any increase in the euglobulin fraction is a characteristic finding which occurs frequently enough to be of diagnostic importance. Corresponding atypical electrophoretic patterns may be equally distinctive.

In this discussion of the medical aspects of tumors of the skeletal system, little has been said about medical treatment. The reason for this omission, of course, is that apart from supportive therapy and amelioration of pain, medical management has little to offer in the treatment of most bone tumors; for the present, the chief function of the internist is to recognize and classify tumors of bone early enough for effective surgical intervention or radiation therapy. There are indications, however, that medical treatment may play a more important role in this field. Estrogen therapy in prostatic carcinoma, androgen therapy in cancer of the breast, the use of nitrogen mustards in the lymphomas, and other recent advances which have been discussed by previous speakers in this series, are examples of the present trends.

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DIAGNOSTIC PROCEDURES IN THE INVESTIGATION OF STERILITY IN THE FEMALE: EVALUATION OF THEIR CLINICAL IMPORTANCE *

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MODERN investigation of sterility and infertility has become a highly specialized discipline, the object of which is to detect the causes responsible for the fruitless mating. As nearly everyone knows by now it involves inquiry into the anatomical, physiological and pathological factors of each partner joined in barren marriage. In many instances search for the cause or causes is analogous to tracking down the "criminal and his accomplices in a detective story" so elusive and uncertain may be the underlying factors and so tenuous the clues. Yet not uncommonly it is a trifling matter, one not ordinarily considered that may be at the basis of the failure to conceive.

A few examples may be cited. There is the couple who through gross misinformation habitually selects the wrong time for "fruitful copulation"—the woman who douches immediately after coitus for cleanliness, one who immediately urinates after the sex act. Couples in their ardor not to miss the favorable time resort to too frequent intercourse thus exhausting spermatogenesis and missing the supreme opportunity, when ovulation takes place. Daily douching with an anti-septic solution without need when local conditions are normal is another cause of failure to conceive.

Unnecessary contraception in the presence of natural barriers has recently been stressed in a special communication based upon an analysis of 686 married women who practiced contraception for varying lengths of time.¹ There are many other such impediments which may be revealed by careful and comprehensive history taking. The suggestive data are not always volunteered by the patient, sometimes coming

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to the surface quite by accident. Correction of errors of sex hygiene may be all that is needed in these cases. Faults of sex hygiene on the male side I leave to the urologists to deal with.

It is obvious therefore that the first step in the investigation of a sterile mating is to get a good medical history of both partners. As I am dealing with the female side of sterility I shall dwell upon the gynecological aspects but many of the constitutional factors are of equal importance in both sexes.

Mumps is of particular etiologic importance. It affects the ovaries as well as the testes. Even mild attacks in adolescence may be followed on one side by amenorrhea and on the other by failure of spermatogenesis. Scarlet fever, streptococcic sepsis and other infectious diseases of childhood may leave the ovaries damaged in later life. Appendicitis of all degrees of severity should not be overlooked as responsible for tubal occlusions and periovarian adhesions. Peritoneal tuberculosis, pneumococcic peritonitis, operative interventions for acute abdominal lesions are other noteworthy data. An attack of vulvovaginitis in early childhood is in my experience not as significant as has been generally supposed. Prolonged and unnecessary local treatments for this condition nowadays happily unnecessary may be responsible for some vaginal atresias and cervical phimosis.

Developmental retardation chiefly physical but also mental, has endocrine significance. Late development of teeth, late menarche and prolonged delay in the menstrual habit are more specifically suggestive of deficient endocrine balance and function. Prolonged uterine bleeding of puberty extending into early adult life is also an important symptom of endocrine imbalance in which the pituitary and ovaries manifest a disturbed reciprocal influence.

Notation of these conditions is significant for formulating prognosis and estimating the contributory causes of sterility.

Dietary habits may well be scrutinized as well as the degrees and forms of exercise. Obesity and malnutrition, especially the latter, play an important role in sterility. The effect in either case is upon the germinal zone of the ovarian cortex reducing markedly the ripening of follicles and inhibiting ovulation. Severe mental strain, close application to college studies without a moderate amount of fresh air and some open air exercise also impair fertility.

Similarly the strain and stress to which female executive heads are

subjected has a baneful influence on their fertility. Strenuous factory work undoubtedly impairs ovarian function also. Chronic lead poisoning and other metallic intoxications; absorption of noxious chemical substances which affect the ovaries particularly must be borne in mind. The more young women and especially the older women still in the reproductive age who are employed in industries which expose them to these toxic substances, the greater will be the general incidence of infertility. Sometimes less strenuous exposure as for example painting in oil, which is indulged in as a serious hobby and not ordinarily inquired into, may have a pernicious effect. Female teachers exhibit a conspicuous lowered fertility, partly due to protracted celibacy, but mostly to the strain of their work.

The matter of age is important as the reproductive ability has long ago been recognized to wane decidedly after the fourth decade of life. Though a substantial percentage of women between the ages of 35 and 45 become pregnant, conceptional incidence is certainly small by comparison with younger women between the ages of 20 and 25. Nevertheless women of the older age group should not be discouraged from taking advantage of a sterility investigation which they deserve and need as much or more than their younger sisters.

The degree of fertility of the parents of the sterile woman and of her sisters and brothers and of the husband's family is of genetic interest but not as a rule illuminating to the clinician. Many of my patients are members of large families and may be the only ones in the family group who have not conceived. More important is the particular mating of the individual and the constitutional and genital status of each partner.

Exceptionally abnormal sex development is duplicated by several members of the same family. For these individuals little if anything can be done.

Nor is the matter of libido, or orgasm, or frigidity, as important in lowering fertility as Kisch, amongst others, has led us to believe. Unless these psychosexual abnormalities interfere with the sex act itself they are relatively unimportant as sterility factors. If, however, there are associated stigmata of under-development, their etiological importance may be considerable. The present writer has encountered women who have manifested definite homosexual tendencies and who have nevertheless been highly fertile; and others with bisexual proclivities have also be-

come easily pregnant. However, systematic inquiry into this group of women may be resumed anew in light of all the sterility factors now recognized in combination with the latest techniques of psychoanalysis.

In the group of secondary sterilities the matter of spontaneous abortions, of premature births, of prenatal and postnatal stillbirths unattended by trauma are data which suggest luetic infection, endocrine or vitamin deficiencies or a combination of these which are ultimately reflected in poor germ plasma—while the serological status of the mates as expressed in the Rh factor may show them to be incompatible. Induced abortion and puerperal infection, especially the former, produce sequellae which are likely to impair tubal patency and ovarian function. Anemia per se apparently does not predispose to sterility and infertility. It is frequently encountered in pregnant women. Pulmonary tuberculosis is notoriously associated with pregnancy.

The exact nature of the deterrent is not always determinable. Yet conception can take place in the presence of cervical cancer, of cervical gonorrhea and as serious a metabolic condition as diabetes, although diabetic women statistically show a relatively lowered incidence of pregnancy and greater tendency to stillbirth. The secondary effects of gonorrhea are predominantly sterilizing. Perhaps more careful clinical observation may lead to clues which biologic methods may eventually utilize to explain the mechanism of at least some of these physical and chemical sterility factors. There is need for greater clinical study and analysis to keep pace with the rapid strides made in biophysics and biochemistry.

While we await such progress we are in a much better position today to evaluate the causative factors than at the turn of the present century. Many here can appreciate the advances that have been made in the examination for sterility. Previously it was customary to examine only the woman. A bimanual examination with or without the use of a speculum or uterine sound was depended upon for the verdict of sterility or fertility. Too frequently it happened that the woman who was told "there was nothing the matter with her" and therefore she could expect to conceive never became pregnant while others who were "doomed" to hopeless barrenness left the gynecologist's office disconsolate but to their surprise and great satisfaction became promptly pregnant.

We have not as yet solved all the causes of sterility even today but

we are more aware of the factors involved.

Investigation of the married partners separately and estimation of their combined index or degree of fertility have been rewarded by greater success than was possible previously. One of the first advances in human sterility was the Huhner test. Huhner popularized in the early decade of the present century, the procedure which was first proposed by Marion Sims in the last century, namely the search for spermatozoa in the female genital canal as a test for male potency. This procedure which is indispensable in the investigation of the childless couple will probably continue to belong to the task of the gynecologist, although the coöperation of the urologist is paramount if further advances are to be made in estimating the procreative ability of the male. Since the Huhner test was established, progress on the gynecological side has been made along several aspects hitherto ill understood or not at all.

The first is the cyclical changes in the vaginal mucosa which are related to estrogenic and gonadotrophic function. The second is the character of the cervical mucus secretion which is also subject to cyclical change under the same influence. The third is the cyclical changes in the endometrium now definitely correlated with estrogenic and progesterone secretions. Though Hitschman and Adler described the histologic changes of the uterine mucosa nearly 40 years ago rediscovering and amplifying, according to Hamblen, the observations of Kundrat and Engelman in 1873, the hormonal significance of these endometrial changes was more fully realized some twenty years later. The fourth step in progress was the realization that the fallopian tubes, previously an indeterminate factor playing as they do an important role in the transportation of ova and spermatozoa, became susceptible of determination first by uterosalpingography and shortly afterward by uterotubal insufflation. The fifth and final step in the progress of the knowledge of the genital sphere was the recognition of the fact that ovulation and menstruation do not necessarily go together; that contrary to the old dictum "without ovulation no menstruation," we now know, thanks chiefly to Corner and his group, to Carl Hartmann, Hamblen, Mazer, E. Novak, Rock and Hertig and many others, that menstruation can take place without the precedence of ovulation; in other words that menstruation can be *anovular*.

The techniques that have been developed to determine the event of ovulation have engaged the serious attention of many workers in the

study of sterility. I should like to consider the progressive steps in the order mentioned.

The vaginal mucosa undergoes cyclic morphologic change similar to the change exhibited by the endometrium. Evidence of this cyclical metamorphosis is based upon (a) biopsies of vaginal mucosa, (b) histological examination of gross sections of vaginal mucosa removed during plastic procedures and (c) studies of the stained vaginal smears, all with reference to the time interval spaced between two menstrual episodes.

The vaginal smear method advanced by Papanicolaou and Shorr with H. Traut and J. V. Meigs as chief protagonists is obviously more practical than vaginal biopsy since the specimen to be examined may be secured by the patient at her convenience and brought to the gynecologist daily or at stated intervals. Despite the hardship entailed by daily or frequent calls at the physician's office the knowledge gained in the hands of experienced histologists is enough to compensate in selected cases for the trouble involved. The reward of this time-robbing procedure is identification of the best time for copulation, namely the time immediately preceding and coincident to and immediately after ovulation. The process is tedious, and requires great experience to interpret the smears. The matter of staining is very important. Should this method prove to be universally reliable it may tend in the absence of other more convenient and reliable methods to be worth while teaching individual women of exceptional intelligence, who are keenly bent upon exhausting every measure to help them conceive, how to stain their own specimens and to interpret them, offering them the facilities of clinic or private laboratories. For this interpretation physicians themselves require special training, which takes much time and effort they may not otherwise be able to spare in a busy practice. The women in question may with more leisure and concentrated interest become adept at reading the vaginal smears.

The object of the study of the vaginal smear is obviously to time coital relations to the most fruitful possible time of the menstrual cycle. This holds particularly for the sub-fertile woman whose menses are habitually delayed but may also benefit women who have no menstrual aberrations. While the male gametogenic defect can at once be ascertained by the examination of his semen, ovulation is "notoriously" elusive, taxing the skill of the experts. As is well known, ovulation can

only be discovered directly by search for ova in the opened abdomen, a formidable exploratory procedure to subject the woman to for this sole purpose, the result of which may hold for that particular month. Incidentally should an ovum actually be found in the tube washings during the laparotomy the patient is in no position under the circumstances to take practical advantage of the finding. The evidence therefore must be indirect and simpler to establish.

A second method of estimating cyclical ovarian uterine physiology is based upon examining the cervical mucus. The role of cervical mucus has been the subject of much speculation for a long time before the present era. It was long recognized that it was either favorable or hostile to the reception of spermatozoa. Only in the last two decades has an attempt been made to show that the secretion of cervical mucus undergoes cyclical change in consistency and in amount and that it subserves estrogenic function. Seguy and Vimeux were the first to insist that at ovulation time the cervix mucus is less viscid, more abundant and is transparent favoring the motility of spermatozoa and fostering their progress toward the tubes. Kurzrok and Miller, Lamar, Pommerenke, amongst others, were especially concerned with this question. The evidence adduced points to a great probability that at the time of ovulation the cervical mucus actually is thinner and more abundant and more favorable for the transmission upward of the spermatozoa. Obviously as a practical measure it shares the same disadvantages in that daily visits and examinations are necessary and entails much skillful observation on the part of the physician. As I have previously had occasion to remark in this connection, the best evidence of favorable mucus is the presence in its environment of actively motile spermatozoa—which, however, can be demonstrated at other times than that of the mid-menstrual interval.

A third procedure extremely telltale for the functional status is that which is afforded by endometrial biopsy. For this procedure only one examination per month is necessary. Advantage is taken of the knowledge gained in the past years by countless histological examinations of endometrial curettings. Here too the changes are dependent upon estrogenic function (estrogen, progesterone) both of which are secondary to gonadotrophic-pituitary function. By means of a small curette with or without suction, such as that devised by E. Novak, several small fragments of endometrium are removed from the surface of the uterine

mucosa, which are then subjected to histological examination. The preferred time adopted by most gynecologists, is one to three days before the menses, or a few hours after the actual onset of the menses, which Hamblen resorts to exclusively. If ovulation has taken place the endometrial glands show the typical secretory progestational phase. If ovulation has not taken place, various degrees of proliferation may be exhibited indicating anovulatory menses.

This procedure has two limitations: 1) whatever evidence the endometrial biopsy affords it is restricted to one cycle and is by no means a positive indication that the next or remote menstrual cycles may or may not be ovular or anovular. 2) It is done too long after the event of ovulation to be of practical use. One positive evidence of ovulation however substantiates the existence of a normal functional relationship between ovaries and uterus in the particular woman in question, a condition of primary importance for her reproductive ability. Obtaining the specimen shortly after the onset of the menstrual flow eliminates the possibility of destroying the occasional impregnated ovum which may be thus rudely removed by the curette. More preferable perhaps is the examination of the menstrual discharge collected during the first twelve or twenty-four hours after its onset in a suitable rubber receptacle properly prepared to prevent deterioration.

A fourth procedure resorted to in the past few years has been that of daily temperature recordings throughout the menstrual cycle. This method first promulgated by Zuck and by Rubinstein has become popular since P. Tompkins made available a convenient chart with tracings illustrating the biphasic character of the temperature. Apparently the shift downward by a drop of 6 to 8 tenths of a degree and a similar rise within 24 hours should coincide with the event of ovulation. This method if established on sufficient scientific grounds by correlating adequate evidence adduced by other methods, especially the actual visual demonstration of synchronous ovulation or of pregnancy occurring as a result of a solitary sex act performed according to the indication of the basal temperature, would prove the most practical and so far the most convenient method of determining the actual event of ovulation.

Other methods such as electrical potentiometric determinations, which gave promise at first, but have later proven unreliable, share the inconvenience of daily visits to the physician's office and special elabo-

rate electrical apparatuses, which render it impractical. Another method which has similar disadvantages is hormonal bio-assay. Tedious, expensive and, as yet, subject to too much variation, bio-assays have been more or less abandoned for practical clinical use, except by a few specialists, by university and pharmaceutical laboratories having extensive facilities and personnel. The same disadvantage characterizes kymographic uterotubal insufflation when employed for this special purpose although it is highly suggestive and of scientific interest. Estimating the glycogen content of vaginal, cervical and endometrial mucosa falls into the same category.

Concerning endocrinopathic factors: The freaks are at once recognized. Subjects suffering from classic endocrine disease have been amply described in the literature. Unfortunately the impression has somehow been gained that these freakish individuals preponderate in the sterility group. Actually they are infrequent and form tragic figures because so little can be done for them. This is not to say however that endocrine disorders do not underlie to some extent many otherwise normal looking patients. It is common experience to see one sterile woman after another who differs relatively little by external appearance from fertile members of her sex. The overwhelming majority of my patients have been women who have presented only the slightest stigmata of heterosexual development or virilism. In this respect we would be rather hard put at present if we should depend on hormonal bio-assays to estimate the degree of maleness or femaleness of sterile married couples.

Concerning uterine hypoplasia, much emphasis has been placed upon the uterine index. The convenient hysterometer of Meaker and of Meigs enables one to get an idea of the relative proportion of the length of the cervix and the body of the uterus. Unfortunately, as I have had occasion to point out before, criteria for hypoplasia have not been definitely established. This is of utmost importance. Apart from the theoretical concept of the undeveloped uterus which may resemble the infant's size to that of the prepubertal and early adolescent size, there are encountered many uteri which appear small upon bimanual palpation but which have a length of from 6 to 6½ cm. or even 7 cm. by actual measurement with the uterine sound. From many measurements of uterine length compared to the uterine enlargement of early pregnancy the length of 7 cm. would represent the fully developed, mature uterus; that of 5 cm. or less a hypoplastic uterus. Due allowance must be made for the general body development, size and age of the patient. The size

of the vaginal portion of the cervix and its configuration it seems to me are of considerable importance, perhaps of greater importance than its proportion to the body of the uterus. The short cervix with quadrangular contour instead of the elliptical contour, particularly when its external surface mucosa is still rugous is the best example of the hypoplastic or undeveloped cervix.

What makes determination of the date of ovulation so difficult as compared to the incomparably simple test for tubal patency for example is first, that the ovum is relatively short lived, its longevity not being more than 24 hours to 36 hours; and secondly, it occurs once in 26:28:30 or more days. The claim of some observers that ovulation occurs twice a month or even three times does not make the task easier. Nevertheless one can hope that some reliable simple method of daily examination for evidence of ovulation may yet be achieved.

A fifth procedure previously unknown but available in the past three decades is that afforded by tests for tubal patency. In 1914, Cary first, then Rubin published their first attempts to demonstrate whether fallopian tubes are patent or not patent by injecting x-ray opaque solutions into the uterus under pressure. Since that time many modifications, both in the substances used and the technique, have been advanced. Without going into the reasons which led Rubin away from the early substances used in hysterosalpingography, the latter was succeeded by uterotubal insufflation in 1919. Subsequently an apparatus was developed which, with suitable recording device, resulted in the method of kymographic uterotubal insufflation, using CO₂ as the gas medium. This method enables us to establish patency, non-patency, partial patency (permeable strictures), spasm, and to record the muscular tonicity of the uterus and tubes.

There are two main uses for hysterosalpingography. One is the x-ray visualization of the cavity of the uterus; the other the demonstration of the lumen of the fallopian tubes. As to the first, its value in the investigation of sterility is indisputable. It enables us to diagnose obstructive lesions within the uterine cavity not otherwise readily or certainly accessible except by uteroscopy. It also affords us some idea of the developmental status of the uterus. With regard to the second, it is claimed that, not only is the question of patency or non-patency thereby settled, but that the exact site of obstruction is thus localized. Without going into detailed comparison, it may be stated on the basis

of a large and adequately controlled experience that this point can also be diagnosticated by kymographic uterotubal insufflation.

In connection with hysterosalpingograms it must be emphasized that they are subject to the same limitations of subjective interpretation, as in any other department of visceral roentgenology. It obviously takes more knowledge and skill to interpret the results than the mere technical x-ray exposure of the film and its development. Critical review of hundreds of films in the light of the findings of kymographic uterotubal insufflation checked by many laparotomy observations and follow-up records have shown that errors in interpretation of the hysterosalpingogram, both with regard to patency or non-patency, are considerable. The second and chief disadvantage is that when non-resorbable or slowly resorbable x-ray opaque substances are used they may and do produce foreign body reactions with nodulations, which cause permanent occlusion of tubes that were previously only strictured.

With kymographic uterotubal insufflation all these points may be established without the deleterious results just mentioned following hysterosalpingography.

Uteroscopy: Efforts to inspect the interior of the uterus were made before 1914. Hysterosalpingography has since then entirely eclipsed uteroscopy. Inadequate instruments and the necessity of introducing irrigating fluid which would reach the peritoneal cavity and carry possible infection were obstacles that discouraged further attempts to improve upon the David type of hysteroscope. In view of perfected cystoscopes especially of the children's type and advances in our knowledge of the capacity of the uterus, its interior configuration and the pressures usually required for gas or fluid to enter and pass through the tubes, and newer effective chemotherapeutic agents, this method of direct inspection of the uterine cavity in a manner similar to that of cystoscopy has been again undertaken the past few years and I may say with encouraging usefulness.

The instrument employed is that of the narrow gauge McCarthy cystoscope with an acorn attached similar to that employed for uterotubal insufflation. The observation cystoscope is first introduced under irrigation with a maximum pressure of 40 mm.Hg. One need only hold the irrigating bottle at a level of roughly 42 cm. above the patient's body to maintain this maximum pressure. With a forward looking lens both uterine ends may thus be inspected as well as the whole cavity.

The catheterizing cystoscope can next be introduced. With perfected plastic materials now available, the time has come for renewal of attempts to catheterize the uterine ends of the tubes, the accomplishment of which was thought impossible twenty-five years ago. It need only be mentioned that this examination can be made as an office procedure.

With uterotubal insufflation, with hysterosalpingography and uteroscopy, we are now in possession of methods of exploration by which the anatomical continuity of the female genital tract can be established and the functional status also.

There remains only the task of determining the anatomical and functional status of the ovaries. Being concealed and not always palpable on bimanual examination their presence is often assumed by the secondary genital and general manifestations of their endocrine function.

The only practical hint offered by all the investigations including the illuminating work of Hertig and Rock on early impregnated ova is that ovulation usually occurs between 14 and 16 days before the next menstruation. In regular cycles it is easy to anticipate this date. When menstruation is irregular the task becomes very difficult. On the other hand advice to have intercourse 16 to 14 days before the next menses even in women who menstruate regularly, is not uniformly rewarded by success. Moreover, contrary to the Knaus-Ogino theory of the safe period many women conceive at "unorthodox" times, even during menses.

If we have the means to establish the mechanical patency or non-patency of the upper portion of the female genital tract thus clearing the question as to free or obstructed transportation of the spermatozoa to and through the fimbriated ends of the fallopian tubes—and the same possibility or impossibility for the migration of the ova, we are as yet in no position to determine the physiological function of the ovaries except by the indirect methods already described.

I. Stein and Arens amongst others have sought to combine hysterosalpingography with pneumoperitoneum produced by transuterine insufflation. The shadows obtained by this combined method do not give sufficient detailed data to warrant its extensive use.

Direct inspection of the ovaries has been made possible without laparotomy in its usual sense in two ways: (1) by abdominal peritoneoscopy and (2) by vaginal coeloscopy. The first method is used by a few workers in this country and abroad. It is fraught with somewhat

more danger than the second. Between abdominal peritoneoscopy and a small exploratory laparotomy there is only the difference of two or three inches which in modern surgery is generally regarded as more or less unimportant. Besides, the few inches added to the incision enable the surgeon to perform procedures which may prove useful to the patient.

On the other hand vaginal coelioscopy has the advantage of direct inspection of the ovaries without so much traumatizing of tissues. The posterior vaginal fornix in the knee chest position is relatively thin and allows the instrument of ready introduction into the cul de sac of Douglas. Accidents are not so apt to occur and if they do, are less serious because they occur in the most favorable position for natural drainage. Its limitations are that the posterior cul de sac must be free of adhesions, a handicap which also obtains in abdominal peritoneoscopy.

By vaginal coelioscopy the size and appearance of one or both ovaries may be demonstrated, and in favorable cases, the presence also of corpora lutea in various stages of development. The presence of periovarian adhesions may also be noted. It is a method which we owe to Decker and Cherry who designated it "culdoscopy" and is well worth employing under proper auspices both for scientific and practical purposes in selected cases. Its importance for the future is obviously to serve as a check upon the effect of gonadotrophic hormones in cases of amenorrhea where it may be repeated twice or possibly three times.

SUMMARY

The diagnostic procedures which have been considered in this paper as constituting steps in the investigation of the woman who complains of childlessness need not all be applied to each case. Many women do not need the comprehensive examination as for example when an obvious minor fault is at once discovered, the correction of which suffices; or when there is present a congenital anomaly not amenable to correction; or when azospermia or tubal occlusion has been demonstrated.

I have considered the procedures *in toto*. A number of these may in many cases be omitted altogether and it has not been my custom to subject each couple to complete investigation at once. Allowed some time, nature can with the proper therapeutic hints accomplish the much desired result.

Investigation can however be underdone as well as overdone. It is

just as erroneous to assume that the husband is "all right" on the say so of the wife, although he is actually aspermic, as it was to accept the old gynecologist's opinion that there was nothing the matter with the wife—although her fallopian tubes were actually occluded. On the other hand it is not necessary in all cases to subject husband and wife to a complete routine physical and laboratory examination, as is insisted upon by some specialists in sterility because the highly specialized techniques are not commensurately rewarded by fruitful results.

For practical purposes a necessary minimum investigation may be adopted which suffices for the majority of cases of sterility. This consists of (1) a good medical and gynecological history, (2) careful general and local physical examination, (3) BMR and other general laboratory blood and urinary examinations, (4) Huhner test and examination of the unmixed specimen of semen, (5) Kymographic Uterotubal Insufflation supplemented when necessary by Hysterosalpingography, (6) basal temperature recording. The essential practical data may be derived from these six steps in the investigation. The others are difficult to carry out or have as yet doubtful practical value. As in all branches of clinical medicine one must in the last analysis exercise clinical judgment in appraising the underlying causes or factors at the basis of the abnormal condition which in the topic under present discussion is genetic failure. Routinization has not in my experience led to more favorable results than judicious selection of the practical measures at our disposal.

In conclusion it should be added that when the minimum investigation as outlined, fails to reveal the faults of fertility then no efforts should be spared to explore all the possibilities of the more elaborate methods of inquiry. There is a special group of sterile couples, about 5 to 10 per cent of all cases, for whose reproductive failure no plausible explanation is as yet to be found. For this relatively small group in particular and to some extent also for the larger group of sterile women much clinical and biologic research remains still to be done.

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CURRENT CONCEPTS OF
FERTILITY IN THE MALE*

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THE acquisition of new knowledge concerning the biochemical constituents of the semen and the metabolic behaviorisms of spermatozoa, suggests the advisability of reviewing this information in respect to clinical applications and to the pursuit of further promising investigations.

The fluid portion of the semen comprises, by far, the bulk of the entire ejaculate. The seminal vesicles contribute the main volume of the discharge exceeding the combined amount from the epididymides, ductus deferentes, prostate and periurethral glands. Analyses of the semen have demonstrated that the fluid is a complex chemical mixture consisting, amongst other elements, of: sodium chloride, phosphates, calcium, sugar, cholesterol, acid phosphatase, ascorbic acid, albumin, globulin, mucin and thromboplastic enzymes. The investigation of Huggins and his associates¹ have demonstrated that the prostate produces little, or no, reducing substances, but elaborates electrolytes and enzymes responsible for the liquification of the semen. Fibrinogen and fibrolysin have been isolated and the lysis of the coagulated semen can be accounted for by their action. It is probable that the coagulation occurs almost immediately upon the emission of the semen from the body but, as yet, this phase of the process is not as clearly understood.

It is difficult to interpret what teleological objective is accomplished in the human by the process of coagulation and liquification of the semen. It is possible that the entire process is merely a phylogenetic phenomenon more clearly represented in the rodents who seal the semen in the vagina by a coagulum called the copulatory plug. However, it is fully appreciated that maximum motility of the spermatozoa is not attained until the lysis of the fresh human ejaculate is completed,

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a process requiring five or ten minutes. The coagulum may offer a protection to the spermatozoa which, for the first time, have come in contact with the utilizable sugar. During lysis they may be offered the opportunity to take advantage of the substrate while being afforded a protection against the acidity of the vagina.

Increased viscosity often has no appreciable deterrent action on the type or duration of motility of spermatozoa. Some specimens of semen having abnormal increased viscosity may exhibit a peculiar clumping or agglutination of sperm resulting in defective motility and an enormous loss of cells due to their entanglement in large clumps. This may represent a faulty operation of the enzyme systems concerned with the production and reversal of the coagulum, but, as yet, the explanation remains theoretical. Additional research may yield valuable means to overcome this relatively rare, but definite, defect in the semen. A promising avenue of investigation remains open.

Experimental observations derived from the study of the metabolism of spermatozoa indicate that the cells have only two known basic requirements. The spermatozoon requires a sugar from which it derives its source of energy, and an isotonic medium furnishing a vehicle for suspension. Ringer's-glucose solution is a simple chemical mixture as contrasted with the impressive array of materials and agents listed above as physiologic constituents of the semen. MacLeod² conclusively demonstrated that spermatozoa suspended in sugar-free Ringer's solution lost motility and retained only minimal metabolism after three to six hours. Furthermore, the addition of glucose promptly reactivated the motility and restored normal metabolic rate. Quantitative analyses of reducing substances in semen have shown that 300-600 mgms. per cent are present, whereas only 20 mgms. per cent appears to be the minimal amount of glucose required in Ringer's-glucose solution for maintenance of normal motility and metabolism of spermatozoa. Nature's twenty-fold, or more, excess of foodstuffs over basic requirements may be another illustration of her remarkable extravagance repeatedly exercised in her allotments for the insurance of adequacy in the task of reproduction. A logical deduction from the above would be that possibly poor motility or early inactivation of sperm could be attributed to the absence or reduction of fermentable sugars in semen. A large number of analyses have been done with this presumption in mind, but, in no instance, was there found to be a deficiency approaching the minimal

requirements. It is of interest to note that a large part of the fermentable sugars of seminal fluid is fructose. The epithelium of the seminal vesicles must have the remarkable ability to select substances from the blood stream, or even perhaps, transform glucose into fructose and deposit the substances into the lumen of the vesicles. The seminal vesicles produce all but a fraction of the reducing substances, and as such they are to be considered vital organs in the physiology of reproduction. Doubtless there is purpose for the unexplained complexities of the semen, and it is our ignorance rather than nature's extravagances which causes our concern.

Much remains unknown about the physiology of ejaculation. A study of the divided ejaculate permits speculation on the emptying processes of the ductus deferens, seminal vesicles and prostate.³ Several men collected the first half of the ejaculate in one test tube and the remainder in a second. Analyses of thirty specimens so obtained are summarized herewith. The initial 39 per cent of the semen contained 76 per cent of all the spermatozoa. The high concentration of reducible substances in the second portion implies that the seminal vesicles emptied during the latter phase of the act. Lactic acid accumulates as an end-product of the glycolytic metabolism of spermatozoa and is found in greater concentration in the denser part of the ejaculate. The motility of the cells is superior in the first portion of the discharge.

From the above, it is possible to infer that, upon discharge of the semen, the ductus deferens empty their ampullae, wherein are stored a dense concentration of sperm ripened for best motility and capable of the highest degree of activity. Thereupon the seminal vesicles discharge their main contribution of reducing substances, along with additional sperm more distally located in the ductus deferens, together with a few poorly motile sperm which may have previously migrated into the vesicles. The prostatic secretions mixed into the combined secretion produce a fairly uniform coagulation. The resultant semen averages two to three cubic centimeters in amounts and, upon liquification, the spermatozoa attack the sugar substrates to obtain energy for motility. Upon deposition into the vagina the semen buffers the hostile vaginal secretions and forms the seminal pool, permitting access and sperm migration into the cervix. Lastly, another caprice of nature must occur, for it seems certain that the sperm rapidly leave the elaborate domain of the seminal fluid and enter the cervical canal, carrying very little glu-

cose with them. If several hours elapse before the spermatozoa reach the ovum, then, on the basis of experimental evidence, a new source of energy must be found in the female genital passages. Recent evidence indicates the presence of ample sugar in the cervical mucosa.

The cellular elements of the semen consist mainly of spermatozoa, together with cells which have been detached from the inner walls of the seminal tract and urethra. The process of metamorphosis by which the mature spermatozoon is produced from the undifferentiated germ cell is familiar to all students of the basic sciences. Recently, clinicians have again had occasion to review and reëxamine spermatic tissue, for the procedure of testicular biopsy has become an accepted diagnostic procedure. Testicular biopsy has been utilized to determine whether the absence of spermatozoa in the semen is due to failure of spermatogenesis or to bilateral occlusion of seminal tracts distal to the tubuli efferentes and proximal to the ejaculatory ducts. The history and physical examination may give clues to the cause of the azoospermia, but often it becomes necessary to remove testicular tissue to establish the diagnosis of either seminiferous or obstructive azoospermia.

The study of tubules of the testes removed from men who are sterile has emphasized several important facts which were known to certain pathologists and histologists, but were unappreciated by clinicians. Outstanding among these is the presence of a thickened peritubular membrane about the seminiferous tubule. It has been noted that the degree of atrophy or regression of spermatogenesis is often in direct ratio to the amount of fibrosis developed in the basement membrane. The blood supply to the active spermatic tissue lies in the interstitial areas outside the peritubular membrane and, consequently, it is probable that a barrier is formed preventing proper nutrition or exchange to these cells undergoing mitosis. In addition to the process of spermatogenesis, it is likely that other important steps take place in the tubules equipping the spermatozoon for its ultimate destination—the penetration of the ovum. Pivotal attention is being focused on the structure of the Sertoli cells, to which it is likely all normal sperm must migrate and attach themselves prior to leaving the testes. The histochemists are using their refined techniques to identify the function of the Golgi apparatus, the Charcot crystals and the cholesterol bodies found in these trophic cells. It is possible that this stage of ripening or maturing is essential to the proper endowment or charging of the sperm with

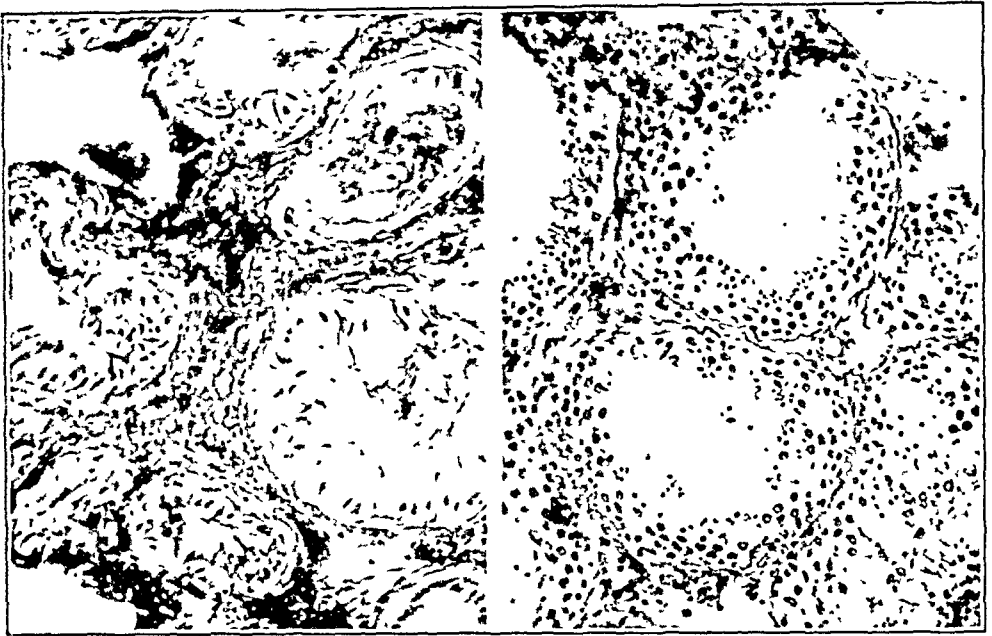


Fig. 1—Thickened basement membrane with atrophy, Sertoli cells only.

Fig. 2—Seminiferous azoospermia due to incomplete spermatogenesis.

trophic substances which may predetermine its future capacity for motility. Thus we may eventually learn that poor motility might be traced to dysfunction of the Sertoli cells.

Another striking abnormality of tissue removed from men who are without sperm in the semen is a disorderly arrangement of the cells undergoing mitosis. Such tissue offers some opportunity for confusion in deciding if the essential fault is an obstructive lesion, or if the azoospermia is attributable to inadequate spermatogenesis. Often a number of spermatids and a few spermatozoa may be found in some tubules. Nevertheless the usual cellular pattern of a spermatogenesis is disrupted and there is a disorganization of the cells undergoing spermatogenesis. The lumen of the tubules are packed with cells detached in the latter stages of spermatogenesis. The peritubular membrane may be of normal thickness.

The cystological changes in the testes have been dwelt upon and illustrated herewith, for there is a growing appreciation that the great majority of defects found in the semen are traceable to malfunction of the testes. It is quite apparent that abnormal sperm morphology is entirely a testicular fault. Reduced numbers of sperm in the ejaculate

likewise may be attributed to defective spermatic activity. Poor motility, however, has often been considered as a defect due to abnormalities of the prostatic and seminal vesicular secretions. It is probable that a definite proportion of men with this fault have the etiological factor in the spermatic tubules and the spermatozoa are incapable of being stimulated into normal activity upon ejaculation. An analysis of 1500 semen specimens⁴ obtained from men whose wives were being investigated for barrenness revealed that, in general, if the cell count were below 60,000,000 per cc. other defects such as motility and abnormal morphology, were more apparent. Semen specimens, in the very low count range, very often exhibited all three deficiencies. Thus, it would appear that faulty spermatogenesis could, in itself, cause oligospermia, increased abnormal forms, and poor motility. Perhaps too often is it assumed that improper motility is evidence of malfunction of the seminal vesicles and prostate.

Accordingly it is pertinent to recall some of the factors exerting an influence or control over spermatogenesis for, by so doing, the rationale of the semen analysis is reviewed and therapeutic inferences are brought into consideration.

It is not beyond the bounds of reality that genetic inheritance may occasionally predetermine spermatic deficiencies. A familiar type of sterility explained by Mendelian laws is the sterile hybrid mule, which is a product of the breeding of the male ass and the domestic mare. A genetic sterility is obviously refractory to any treatment, yet must be considered as a clinical possibility in the human.

There is no evidence that the testes undergo specific changes incident to ageing similar to menopausal changes in the female. Engle⁵ found abundant spermatozoa in the testes and ducts of more than one-half of the men past seventy years of age. The testes share the physiological degenerations of senility, such as arteriosclerosis, but no specific alterations associated only with chronological ageing have been identified. Consequently, no serious impairment of the fertility of the middle aged man can be attributed as due to ageing alone.

Nutrition, and its relation to the physiology of the testes, has been studied in detail in the laboratory. Vitamins, minerals and the amino acids are the principal agents tested in the experimental animals. Deprivation of Vitamins A and E has proven to precipitate severe atrophy of germinal epithelium. Vitamins B-complex, C and D are less specific

and effects vary according to species. The amino acids tryptophane, arginine and lysine may be essential for spermatogenesis. The clinical application of this information is restricted for animal tests exhibit marked variation as to species. Individual variation in vitamin utilization in the human is fully recognized. An optimal diet for one individual may be minimal or deficient for another. Intermediary metabolism and the interrelationship of endocrines and vitamins are now appreciated factors in metabolism of vitamins. Some clinical observers suggest that B-complex, or A or E may occasionally benefit poor motility and spermatogenesis, but this is by no means an established clinical fact.

Increased body temperature has conclusively been demonstrated to depress spermatogenesis. The atrophy of cryptorchid testes is well known, presumably from the adverse effect of 2° elevation of temperature over the normal scrotal environment. The clinician should be alert to examine for migratory testes which, in some men, frequently ascend into the warmth of the inguinal regions with change of position. The author is convinced that decisive improvement in the semen has followed the use of measures to prevent the testes from migrating out of the scrotum and into the inguinal canal.

Little precise knowledge is known of the pathology concerning the destructive action upon the testes of the virus producing mumps. It is now known that the epididymis is tremendously inflamed in the acute stage of the so-called "mumps-orchitis," and that the infection which apparently only involves the post-pubital male is in reality an epididymal-orchitis. This infection is undoubtedly the most common and disastrous acute inflammation affecting the testes in the adult. There is no known preventative treatment except the conferred immunity derived from a prepubital attack. The frequent testicular atrophy following severe inflammation of the scrotal contents is well known. Personal observation of men having only clinical parotiditis revealed that several had definite tenderness of the scrotal contents without manifest swelling and local redness of the skin. They may have escaped a clinical diagnosis of epididymal-orchitis, complicating mumps, but the unproven suspicion exists that such might have been a mild type of involvement not without injury to the germinal epithelium.

The deleterious effect of irradiation upon the testes is fully recognized. The arrival of the atomic age ushers in a new appreciation of such danger, for mass sterilization by atomic warfare is now a known

reality. The use of fission material for industrial sources of energy will doubtless be exploited even if atomic energy is prohibited in future wars. Therefore, a new industrial hazard will deserve attention.

The usual consequence of obstruction is atrophy of the secreting organ so affected. The testis, however, retains both its secretory and spermatogenic capacities despite occlusion of the genital passages in the epididymides and ductus deferens. This allows reparative surgery to be employed to relieve the occlusions and reestablish the patency of the tract upon the supposition that the testes have continued to produce spermatozoa regardless of the length of time the blockage has existed. The operation of vaso-epididymal anastomosis leaves much to be desired, but, when properly employed in appropriate cases, the achievements, when attained, are spectacular and gratifying to those whose sterility is cured. The risk is negligible and, if the procedure fails in purpose, the individual is none the worse than prior to operation.

The problem of the interrelationship of the testes to the other glands of the endocrine system has received enormous attention. The mass of evidence shows that the pituitary exerts a profound effect on the testes and that properly functioning pituitary gland is as necessary for the survival as for the formation of sperm. The thyroid and adrenals, either directly or indirectly, are likewise involved in the endocrine control over the testes. Suffice to state, for this discussion, that there is no effective hormonal treatment for advanced degeneration of spermatatic tissue, and that no single hormone or combination of hormones can be regarded as specific for spermatogenesis.

The results of treatment utilizing thyroid substance has won more universal support from the clinicians than any other product of the internal glands. The gonadotropins have had wide usage, but only in exceptional instances are reported as being beneficial. They had best be employed only as measures of last resort. There is no accepted rationale for the use of testosterone propionate which, in the conventional dosages, depresses spermatogenesis. It is with great expectancy that the clinician looks to the research laboratory for future aid in endocrine therapy. Specific discoveries consonant with human physiology, refinement of hormone products, and evaluation of the limitations and indications for organotherapy are essential to the establishment of satisfactory hormone treatment.

It is difficult to provide precise data supporting the theory that

environmental influences producing fatigue, nervous tension, anxiety and overwork are harmful to spermatogenesis. These factors, coupled with the use of alcohol and tobacco, are frequently encountered in the life of the city dweller. Autopsy evidence has proven that the state of spermatogenesis was proportioned to the duration of the disease causing death. Complete testicular atrophy was common following chronic debilitating illness.⁶ Susceptible individuals with lowered fertility states are probably injured by excessive fatigue, nervous tension and intemperant use of alcohol and tobacco so that the problem resolves itself into one of individual reaction. Correction of such faults is an integral part of a program designed to promote the best of bodily health and function which is to be shared by the gonads.

It is apparent from this brief discussion that we are as yet only on the threshold of a full appreciation of many vital details of the physiology of the male genital system as related to reproduction. The problems are not those of any one specialty alone, but rather are filled with embarrassing riches to all whose inquisitiveness seeks new ventures. The anatomists, biochemists, histochemists, physiologists, endocrinologists, internists, gynecologists, and urologists have special interest and access to the field, and their combined efforts are essential to the progress which will surely come.

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ORGANIZATION AND ENROLLMENT IN
SECTION ON MICROBIOLOGY

THE Fellowship of the Academy formally approved the organization of the Section of Microbiology at the Stated Meeting, May 1, 1947. The action followed the request submitted to the Council of the Academy by Drs. O. T. Avery, S. Bayne-Jones, M. W. Chase, R. Cole, A. R. Dochez, R. Dubos, K. Emerson, J. Freund, J. Furth, F. Glenn, G. I. Hirst, J. G. Hopkins, F. L. Horsfall, Jr., C. Jungeblut, J. G. Kidd, C. M. MacLeod, J. F. Mahoney, W. McDermott, J. M. McLean, P. McMaster, F. L. Meleney, H. E. Meleney, H. Most, C. Muschenheim, R. S. Muckenfuss, P. K. Olitsky, E. L. Opie, C. P. Rhoads, T. M. Rivers, P. Rous, G. Schwartzman, W. M. Stanley, and H. M. Zimmerman.

The organizers of the Section will serve as officers pro tem until the official elections in May 1948, as follows: Chairman, Gregory Schwartzman; Secretary, Harry Most; and Members of Advisory Committee, Rene J. Dubos, Frank L. Horsfall, Jr., John G. Kidd, Colin M. MacLeod, and Ralph S. Muckenfuss.

The main objectives of the Section shall be to encourage exchange of information among the microbiologists and to facilitate liaison between clinical and laboratory investigators. The programs will be divided into two major groups, namely, those of special nature, primarily intended for the microbiologists; and those of mutual interest to microbiologists, investigators in allied sciences and clinicians. The scope of the Section will embody the following:

1. Bacteriology, Mycology and Parasitology; 2) Viruses and Rickettsiae; 3) Maladies of unknown and uncertain etiology, possibly of infectious origin; 4) Immunology; 5) Chemotherapy; 6) Pathology relative to Microbiology; and 7) Methods of Study adopted from related Sciences, as applied to Microbiology.

Fellows of the Academy interested in microbiology are cordially invited to enroll as members of the Section. This may be accomplished by letter to the Secretary of the Academy requesting such enrollment. As membership in two scientific sections at one time is not permitted under the By-Laws of the Academy, a Fellow desiring to become a member of the Section on Microbiology must tender resignation from membership in the Scientific Section in which he is enrolled, at the same time that he requests membership in this new Section.

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



OCTOBER 1947

HARVEY CUSHING'S EARLY TRAINING*

1887-1900

JOHN F. FULTON

YOU have asked me to speak of Harvey Cushing. After some consideration I have decided that it would be unwise to attempt to touch on all phases of his career and that it would perhaps be more interesting to you to hear something of his early years since they are little known.

The tenth child of a busy Cleveland physician, Harvey Cushing was born on 8 April 1869. His great-grandfather, David Cushing, was a country doctor who lived in the now vanished town of Stafford Hill (Massachusetts) in the Berkshires. David's son, Erastus, records that David was a collector of books and a number of the volumes in his library have come down by direct descent to Harvey Cushing's collection. Erastus, also a physician, finding that the population of Stafford Hill and South Adams (to which he later moved) was dwindling, migrated with his small family to the Western Reserve of Connecticut—that tract of land which became, except for that part lying under Lake Erie, the state of Ohio. He arrived in the village of Cleveland in October 1835 and set himself up in practice. His son, Henry Kirke, the father of Harvey, then only ten years old, was in due time sent to Union College

* Lecture to the Historical Section of The New York Academy of Medicine, 20 March 1946

and later to Philadelphia to complete his medical studies. Shortly after his return to Cleveland to practise with his father, he married Betsey Maria Williams, the daughter of another pioneering family who had moved to the Western Reserve from East Windsor, Connecticut.

Of the ten children of Henry Kirke and Betsey Maria, seven reached maturity. The eldest, William, was a lawyer; Edward, who was seven years Harvey's senior, became a well-known pediatrician in Cleveland; a third brother, Henry, occupied the Chair of Geology at Western Reserve University; and all had unusual intellectual interests. All, or nearly all, were addicted to collecting—it little mattered what: stamps, coins, leaves, butterflies, etc. Harvey recalls that in his younger days their house in Cleveland was cluttered with albums filled with insects and botanical specimens of every description.

Evidently certain traits of Harvey's character became manifest at an early age, for when less than six the following jingle was perpetrated upon him at a family party:

"Pepper Pot, Pepper Pot, when you were young
They tell me you had a most fiery tongue."

After attending a small private grade school, Cushing entered Central High School in February, 1883, at the age of thirteen years and ten months, and was graduated on Friday evening, 24 June 1887. Dr. J. J. Thomas, one of his classmates, recalls that Harvey, on entering school, was "a short, chubby little fellow, wearing short pants and a little bob-tailed coat, very fashionable at that time for young boys." He and Thomas took the classical course at "Central," and Cushing stood eleventh in a class of eighty-three students, with a final average for the four years of 89.19. In examining grades in individual courses, it is interesting that Cushing stood very high in Latin, which he had studied throughout his four years (average 92); rather less well in Greek, which he had studied for the last three years; and was poorest in English history, in which he scored the grade of 75 during his first year. He was president of the class during his senior year, and at the class entertainment on 16 December 1886 he was on the program as giving a tumbling exhibition with a classmate, as well as taking the part of "Mr. High-flown" in the class play.

During his high school years he had the good fortune to come under the influence of an outstanding teacher, Newton M. Anderson. Mr. Anderson, after graduating from the University of Ohio, was employed

in 1879 by the Bell Telephone Company to install the first telephone exchange at Liège, Belgium. Returning to the United States in 1881, he became an instructor in physics first at the University of Ohio and then at Central High School in Cleveland. Here he began to agitate almost immediately for a course in manual training. Harvey had taken physics under him in 1883-1884 and had assisted him in the apparatus room where he had received some instruction in the use of tools. The following summer (1884) Anderson took Harvey and three of his cousins up the lakes on a fishing expedition, spending most of the summer at a small farmhouse near Sault Ste. Marie. On alternate mornings Anderson took two of the boys down the river to fish, making them row back against the current. The following winter (February 1885) he bought an island of some twenty-five acres, situated in Lake Huron near the Sault River, to which he took the boys during the summer of 1884, along with a number of others from Cleveland, some fourteen in all. To this camp Cushing returned in the summers of 1886 and 1887, and his first letters that have been preserved date from these camping expeditions. In an appreciation of his cousin, Perry Harvey (later his roommate at Yale), Cushing gives a vivid description of the camp:

To this island we gave the name Maskenoza—the Indian word, I believe, for a pike, which it somewhat resembled in outline—and there we passed most of the following summer [1885], felling spruce with which to build our camp, cooking our own meals, supplying with gun and rod most of our provender, exploring the neighboring country so full of border history, and in leisure time surveying and mapping our small domain.

That winter a staunch 42-foot schooner was built in which, on the eagerly awaited close of school, eight of us sailed from Cleveland to our beloved island, another eight having preceded by steamer to get the camp rebuilt and in running order before the arrival of the schooner with its crew.

In a letter to his mother from Maskenoza (12 August 1887) he writes: "I wish I had brought up a butterfly net this year, for there are more on the island than I have seen before. There is a chrysalis formed on the rafters right over my bed and yesterday Jack brought in a big hawk moth caterpillar, but we could not find out anything for him to eat. So today I let him go as he was getting very meagre. One of the boys brought in the funniest shaped skull I ever saw, which is not

saying much, but we could not imagine what it was so I have preserved it to show to father."

Anderson was convinced that the development of manual dexterity played an important part in the intellectual training of boys, and all of Harvey Cushing's contemporaries in Cleveland have insisted that this early training contributed notably to the shaping of his subsequent career as a surgeon. In referring to Anderson, Mr. Allyn F. Harvey writes: "For myself I can say that he drilled us very thoroughly in the handling of small boats, propelled by oar or paddle, up to thorough ability to handle a 46-foot schooner yacht; he taught us a lot about being independent and made us so by the duties he inflicted upon us during these summer vacations. We were all undoubtedly better disciplined and better prepared for life from the teachings of this man, and from association such as we had with him." And Cushing recalled: "We embryo carpenters progressed to a course of wood-turning with lathes and a year later to metal work at a forge—like so many blacksmiths learning to strike when the iron was hot, the best possible cure for youthful indecision."

Cushing's mother had a kindly nature and she understood Harvey's impetuous ways, but his father was a Puritan much worried about the flesh and the devil, and when Harvey entered Yale he made him agree not to smoke, drink, or consort with those of easy virtue, and above all things, he must not indulge in intercollegiate sports. Harvey, an outgoing Middle Westerner, found himself drawn into the swing of undergraduate activities at Yale within a few days of his arrival in New Haven, and he soon had distinguished himself at the gymnasium in feats of tumbling and had exhibited exceptional prowess on the parallel bars. He was also fond of turning backward somersaults off a six-foot ledge beside the front door of the gym with a lighted cigarette in his mouth. Before he knew it, he had been selected to play shortstop on the freshman ball team, and his batting record proved so unusual that he was promptly put on the varsity nine the following year.

He had kept his indulgence in sports somewhat in the background in his letters home during the first year, and when eventually his father discovered that he was moving around the country with the varsity team and that he was scheduled to go, of all places, to Cambridge, Massachusetts, the floodgates of paternal wrath were loosened, and Harvey found himself in the awkward position of possibly being cut

off from his only source of funds. Henry Kirke Cushing never believed in giving Harvey enough at one time to carry him a whole month—this might lead him into temptations other than intercollegiate sports. Harvey, accordingly, was obliged to send a meticulous expense account every week or two and his funds were never replenished until his last cent had been spent and accounted for.

One of the arguments he offered his father in favor of his playing baseball was the great social advantage of being permitted to sit on the Yale Fence, an honor accorded only to those who had played on a winning Yale team, particularly one which had vanquished Harvard. Henry Kirke did not appear to be particularly impressed by Harvey's ingenuous argument, but he finally sent him his allowance with further stern warnings about scholarship and good behavior. His mother meanwhile had slipped him ten dollars on the side.

His parents possibly had some awareness of their son's unusual talents, for each one preserved separately, and probably unbeknownst to the other, every letter that Harvey wrote from Yale, from the Harvard Medical School, and finally from Johns Hopkins—and he generally wrote to each of them every Sunday, except when there was a crisis such as being "broke," in which case he wrote or telegraphed in the middle of the week. These letters, more than a thousand in number, have all been deciphered and transcribed, and since they give details of his course work both at Yale and at the Harvard Medical School it has been possible to reconstruct educational practices in those days. From these letters also one can trace, week by week, Cushing's rather slow emotional and intellectual development. At Yale he was essentially undistinguished as a student, for he devoted the greater part of his time to extracurricular activity. He became a member of one of Yale's secret senior societies, which he took with the utmost seriousness. "I don't know whether you or any one, except a Yale graduate," he wrote his father, "knows what it is to get an election to Skull and Bones or Scroll and Key. It is the one, the greatest, honor a man can receive in college and is the one thing more than any other sought after by everyone from the time of entering college to senior year and unless I can get an election through athletics I am afraid I will be left out." Later he wrote again: "I won't attempt to tell you what fine things the Senior Societies are acknowledged to be, what a position they hold in the College World and what good they do a man, for if you don't already

know something about it, it would make too long a story. . . .”

It was not until his senior year that he made up his mind to study medicine. Before that time he had thought of architecture and had considered opening an office in New York with his classmate, Grosvenor Atterbury. But Russell Chittenden, who had recently established a laboratory of physiological chemistry at Yale, aroused Cushing's interest in physiology and bio-chemistry during his senior year—an interest easily traced in his notebook of Chittenden's lectures, which contains, incidentally, some unusual sketches of lucine and cholesterin crystals.

It is not clear when Cushing became aware of his artistic talent—but he had had drawing lessons while still in Cleveland. At all events, during his senior year at Yale we find admirable, freehand diagrams exhibiting unusual artistic capacity. During his years at Harvard he sketched continuously. His histology notebook is of itself a work of art, but in addition to laborious drawings over which he no doubt spent much time and energy, he could also catch a likeness with lightning speed, and he was able to convey the whole gamut of human emotions and sensations with a few strokes of his pen or pencil. At clinics he almost invariably drew sketches of the more interesting patients—this to fix them in his memory, both as individuals and as cases exhibiting particular physical signs.

During his medical student years he frequently went off on trips with his family, particularly his brother Edward, and the diaries of such journeys were invariably illustrated with innumerable drawings, many in a light vein, others depicting interesting landmarks and panoramas.

Cushing left Yale in the summer of 1891 and after a vacation in Cleveland he settled on West Cedar Street in Boston, entering the freshman class of the Harvard Medical School, then situated on the corner of Boylston and Exeter Streets. Before he had opportunity to investigate Bostonian dens of iniquity he received another of his father's timeless letters of advice:

. . . The taking up of new threads in a great new city is a trying, and discouraging process. You can imagine what it is like to one who must do it without help from letters and friends. . . . You will undoubtedly find every day now making you more at home in your new work. And as it is likely to be the front entrance into the work of life, deliberation, constancy, zeal and painstaking endeavor should

mark each day.

Be careful with whom you make acquaintance. It is not every bright and agreeable man that it is safe to tie to. Men go astray in great numbers (even at your age and older) under the temptations of one kind and another that insidiously beguile. No one, I suppose, deliberately goes to the bad, but one step leads to another until deep water is unexpectedly attained.

Playing cards for money, tippling, and the frequenting of haunts of immoral women are the three chief ways in which young men have wrecked themselves in my observation. So far as my observation goes, I have come of late to the conclusion that there is a growing laxity of morals in these regards in the present day. . . .

At Harvard, Cushing worked as hard as he had played at Yale, and almost immediately he became a marked man in his class. One of his contemporaries, Charles Russell Lowell Putnam recalls:

. . . From the day his class was turned into the dissecting room, Cushing became as *eminent* among his fellows as he continued to be among his colleagues throughout life. His first "part" was a right upper extremity, and before a day was passed all the students as well as the teachers were watching the progress of Cushing's dissection. Dr. Mixter had placed him near a window, which in the old gaslighted room was important, and groups of two's and three's often came for a few minutes at a time to watch. Cushing himself talked little. First he sharpened his scalpel carefully and frequently, then he raised his skin flaps so as to keep as many of the cutaneous endings of the nerves as possible intact. At the end of three weeks, he had not only his intercosto-humeral intact, but a multitude of anastomoses from the clavicle to the finger tips. He took the same care of the tissues to avoid drying as he afterwards took in his cranial operations. I should say that he showed his professional preëminence from the start. After the early weeks, he began to talk freely to his fellow workers—but first he stated his intentions. "I have decided to be a leper," he said, and with that phrase he refused practically all social invitations that would have wasted his evenings. . . .

Cushing also quickly distinguished himself during his clinical years, but in January 1893, in the midst of his second year, he had an accident that almost caused him to withdraw from the study of medicine. Substituting for Frank Lynam he gave an anesthetic to a patient with a

strangulated hernia being operated on by Dr. C. B. Porter, and the patient died before the class. He was greatly upset and decided to withdraw from the school, but Porter dissuaded him. Thereupon he and Amory Codman, likewise dissatisfied with the procedure for giving anesthetics, between them worked out a system of continuous recording which enabled both the anesthetist and the surgeon to tell at a glance the condition of his patient, as indicated by pulse and respiration. There was no method available at that time for estimating blood pressure, so that when Cushing several years later saw the Riva-Rocci pneumatic device for recording human blood pressure at Pavia in Italy, he seized upon it and brought it back to the United States. Thereafter his ether charts, as the anesthetic records of Codman and Cushing had come to be called, included a continuous blood-pressure record in addition to pulse and respiration.

On the 8th of November 1945 the fiftieth anniversary of Röntgen's discovery of the X-ray was celebrated in various parts of the world. In the six weeks that followed his first observation Röntgen worked feverishly and established beyond all peradventure of doubt that a Crookes' tube, when activated by a static machine, emitted rays that readily penetrated the fleshy parts of the body without passing so readily through the bone. His announcement of his discovery was made at the end of December 1895 before the Würzburg Academy of Science, and the text of the paper was printed a few days later in its Proceedings. The *Boston Medical and Surgical Journal* received news of the discovery early in February 1896 and in the number for the 13th a detailed account appears, accompanied by an X-ray photograph of the hand. Two days later Cushing, who was then an intern at the M.G.H., wrote enthusiastically to his mother:

Everyone is much excited over the new photographic discovery. Professor Röntgen may have discovered something with his cathode rays which may revolutionize medical diagnosis. Imagine taking photographs of gall stones in situ—stone in the bladder—foreign bodies anywhere—fractures &c. &c. Mary Crehore sent me two photographs, one of a hand showing in a most mysterious manner the bones of the hand and a ring on the finger which were outlined in a misty way by the normal outlines of the hand. The other of a fracture of the forearm showing the bony displacements. It's fearfully uncanny. We won't be able to have any secrets if people can take

photographs through stone walls &c. Some letters have come from the men abroad telling of the wonderful things they are doing in Vienna with the X-rays."

There is no indication in this letter that a tube was as yet available at the M.G.H. Dr. Codman, writing many years later, states that John Collins Warren brought back a tube in the spring of 1896, but the tube used by Cushing at the M.G.H. appears to be one that he himself had helped to purchase, as is indicated by the following passage in a letter of 10 May to his mother: "We have at last succeeded in having an X-ray machine put in for which I have subscribed largely and hope the conservative staff will ultimately remunerate us for it. It is great sport—very useful in the Out Patient to locate needles, &c. We could look through the chest readily this morning—count the ribs—see the heart beat—the edge of the liver, etc. I will send you some photographs." From this one must infer that a tube or tubes had been in use at the Hospital for some weeks. Dr. Codman, writing in May 1940, mentions that Dr. Warren had probably obtained his tube not from Röntgen, but in England where the focus tube was actually developed.

Dr. Walter Cannon's celebrated work on movements of the gastrointestinal tract, carried out when a first-year medical student, had commenced in December 1896 and was unrelated to Cushing's earlier clinical studies with the X-ray, for by that time Dr. Cushing had already gone to Johns Hopkins where he had begun a period of service as Halsted's Assistant Resident in Surgery. Cushing took his X-ray tube with him and inaugurated X-ray studies at the Johns Hopkins Hospital. His first clinical report is based on his X-ray studies and it is of some significance in his career, since it dealt with the localization of two neurosurgical lesions—bullets, as it happened, lodged in the vertebral canal beside the spinal cord. These early plates, showing the position of the missile, are surprisingly clear when one considers the primitive tube which Cushing was obliged to use and the fact that the tube was activated by grinding an ancient static machine for some twenty minutes—an interval somewhat too long for a patient to hold his breath!

For four years on Halsted's service Cushing worked incessantly and he found time to make a series of some twenty clinical reports, beginning with his paper on gunshot wounds describing two patients, both of whom had sustained Brown-Séquard lesions of the spinal cord similar to that sustained by General Patton. This was followed by

reports on the surgery of typhoid perforation, local anesthesia with cocaine, a splenectomy for primary splenic anemia, and an important paper describing a method of extirpating the Gasserian ganglion.

The experience at Hopkins proved a particularly valuable one to Cushing, for on account of Dr. Halsted's indifferent health much of the responsibility of his surgical service, both in connection with operating and teaching, fell upon the shoulders of his Resident. It must not be forgotten that Halsted and Osler were responsible for inaugurating the assistant resident-resident system in American medical education. Before that time a promising young surgeon, after a year's internship, during which he might or might not have had opportunity to carry out a surgical procedure himself, was taken on as a junior attending surgeon who then proceeded to gain experience in surgery at the expense of the public. The resident system tended to change all this, for it spread little by little throughout the country. Cushing and Christian were chiefly responsible for starting it in Boston, when the Brigham Hospital was established, and from then on it passed, sometimes from Baltimore, but more often from the Brigham and other Boston hospitals which had fallen into line, to other medical schools, particularly the large state schools in the Middle West and Far West. It has had the effect of placing medical education in the country at large on a plane far higher than that in any other country in the world, not excepting Great Britain. It would be a mistake, however, to believe that the residency system is the last word in medical education. In the first place it has not been universally adopted. For many years the New York schools have held out against it. Your schools have interns and many have assistant residents, but the more prolonged period of training of the residency, so essential for a complete surgical education, has until recently been largely avoided.

Throughout his life, Cushing took a lively interest in all phases of medical education and he was one of those who, though himself a physiologist with a keen interest in all the preclinical sciences, believed that preclinical studies had come to be overstressed in the average medical student's curriculum and that it was highly important to bring students into touch with clinical problems at the earliest possible moment in their medical career. To this end he instituted, first at Hopkins and later at Harvard, a course of Saturday morning clinical lectures for first-year students. He believed that this gave them a more active mo-

tivation for work in general and for their preclinical studies in particular because they were able, through seeing clinical problems, to appreciate the application of their anatomy, physiology, and pathology. In 1925, when called upon to help dedicate the new Sterling Hall of Medicine at Yale, he rather startled his colleagues by comparing the curriculum which Yale and Harvard were then offering students to a heavy-walled cathedral in which the architects had expended so much on the foundations that they were unable to provide a roof. On another occasion, when feeling frustrated over having failed to introduce some improvements in the medical curriculum, he exclaimed that trying to induce his colleagues to alter the curriculum was a little like trying to move a cemetery.

Cushing's first four years in Baltimore had passed quickly and while he was eager to settle down (he had been in love since 1892) Osler and Welch prevailed upon him to spend a year abroad, rounding out his education in some good European laboratory or clinic. He had made one trip abroad with his brother Edward in 1894, but this had been a brief holiday trip of a few weeks and he had not had opportunity to absorb anything of European life or culture. He accordingly sailed late in June 1900 and spent a busy month in England under Osler's wing seeing libraries, hospitals, and attending a round of social functions centering about the Centennial of the Royal College of Surgeons. Osler saw to it that he was invited to the principal gatherings and through that circumstance he was brought into contact with the most prominent figures in contemporary British medicine. In August he crossed to Paris where he spent another week attending meetings, this time the XIIth International Medical Congress which had been organized with all the elaborate continental flourishes of a pre-war gathering. This gave him an opportunity to see and meet many of the important physicians and surgeons of the European continent. He stayed on in Paris for a month, visiting the French hospitals and polishing his French. In October he went on to Lyons, where he was profoundly impressed by the ophthalmologist, Louis Dor, and his erudite father. From Lyons he went to French Switzerland and passed several weeks with César Roux from whom he learned about Swiss thyroid surgery; he also saw some first-rate surgery of the gastro-intestinal tract.

By November he had reached Berne where he settled down for six months, working in the physiological laboratory of Hugo Kronecker,

and in the general surgical clinic of Theodor Kocher. Kocher had never encountered anyone quite like Cushing and for a month he treated the self-assured young American coldly and procrastinated about suggesting a problem on which to work. Cushing grew more and more impatient and by the end of the month he had decided to leave Berne and try his luck in Heidelberg. He had not yet met Kronecker. On advice from his friends he called on the great physiologist and Kronecker, being a much less austere man than Kocher, received Cushing with great warmth and at once made a place for him in his experimental laboratory. Kronecker apparently reassured Kocher about Cushing—he had met self-confident Americans before—and he informed Kocher that if he would formulate a problem for Cushing, Cushing might conduct his studies in the physiological laboratory. Kocher forthwith asked Cushing to investigate the relation of intracranial pressure to systolic blood pressure. As it turned out, he could not have set a problem more suited to Cushing's taste or resourcefulness. Within a few weeks he had developed a procedure for observing the cerebral vessels directly through a window skillfully placed in the skull and, through a second opening, he was able to alter the level of intracranial pressure by raising a drop bottle slung on a pulley from the ceiling of the laboratory. In 1931 when I visited the physiological laboratory at Berne, Professor Leon Asher, Kronecker's successor, showed me with great pride the pulley on which Cushing had slung his pressure bottle thirty years before. The pulley had apparently made a profound impression in Berne because Cushing had screwed it into the ceiling without consulting the Professor.

These studies were finished late in March, following which Cushing went down to Turin in Italy where he spent a month with the Italian physiologist, Angelo Mosso, repeating on dogs the intracranial pressure experiments which he had carried out in Berne on monkeys and cats. He then made a "grand tour" of the Italian hill towns during which he followed the trail of Andreas Vesalius who became something of a patron saint.

He returned to Berne in June to write up the results of his experiments and once again came up against the entrenched continental custom of the professor writing the pupil's paper. It had happened first when Kronecker had called him into the laboratory one evening for the purpose of writing a preliminary report on his results. With sleeves

rolled up and a large pot of coffee beside him, Kronecker began to dictate the text of the paper in German. Harvey Cushing politely but firmly interrupted him, saying, "If you write the paper, it will not be mine and I would not feel free to sign it." After a two-hour argument, Cushing wrote the paper himself. Kocher likewise expected to write up his findings, and we find H.C. writing home: "Most extra-ordinary experience with K. who wished to go over my Arbeit before his departure for Glasgow. Planned for an all-night session, to my astonishment, and then proceeded to write the article as I went over my findings. This I told him was not my way and we had some pretty serious words, fortunately avoiding rocks. Apparently *Selbstständigkeit* is an unusual quality. I was pretty plain with the Professor and told him he could write the article as his, or if he chose to have me publish it, I would do all the work which he could correct and alter as much as he chose." This he did and although doubtless Kocher and Kronecker were both amazed and chagrined at this manifestation of "American ways," it is possible that they were secretly amused, for they remained on friendly terms with their young student as long as they lived.

After more travel on the Continent, Cushing crossed to England where he spent July in the laboratory of Charles Sherrington, the eminent physiologist, who had attracted wide notice through his work on decerebrate rigidity and the functions of the sensory nerves to muscles. He was also beginning a detailed study of the motor area of monkeys and anthropoids. Cushing arrived at a psychological moment in Sherrington's epic research and had the rare opportunity of operating on the brain of both a gorilla and an orang-utang. Sherrington was grateful not only for this surgical assistance, which Cushing was well qualified to give by virtue of his training with Halsted, Kronecker, Kocher and Mosso, but also for the remarkably clear drawings which he made of the anthropoid brain.

During this brief but fruitful stay in Liverpool, Cushing met Alfred Fröhlich of Vienna, then working in Sherrington's laboratory. This was just prior to the time that Fröhlich was to publish his memorable paper describing the syndrome which still bears his name. Cushing left an amusing account in his diary of an expedition with the Fröhlichs to the Isle of Man, made with a view to studying problems of inheritance in tail-less cats. He returned to Baltimore in August 1901 and settled down at the Johns Hopkins where he was to stay until he went to

Harvard in 1912.

Throughout his life Cushing firmly believed that a good surgeon must first become a good physician. His specialization in the surgery of the brain and the spinal cord was therefore based on thorough, early training in the field of general surgery. When he came to the end of his career he had more than fulfilled the promise and ambition of his youth and we can call him scientist, pathfinder, artist, writer, bibliophile, and above all, "a good doctor."

Discussion: ARTURO CASTIGLIONI

I am glad to be able to say some words to you tonight when we are honoring Harvey Cushing. John Fulton has just written his biography, a book which will have, I am sure, a place in the library, not only of every American surgeon and student and of all the people who knew and loved Cushing, but also among the books of all who are interested in learning the history of the development of the personality of a great surgeon and of a great artist. Dr. Fulton has spoken to you of Cushing as a young man, of the years in which his personality was moulded, and has given a brilliant account of this period. Our Chairman and friend, Dr. Leona Baumgartner, whose work I have appreciated for a long time, wrote some years ago some interesting pages about Harvey Cushing as a book collector, and she would surely be more able than myself to describe to you this part of the activity of Cushing. I have only one right to speak on this subject, that is that I had the privilege of knowing Harvey Cushing and of loving his work. I met him several times in Italy, the country he knew and loved, and I had the privilege of discussing with him many things in which we had a common interest. A book lover and a book collector myself, I hoped to be able at last to have my books, very modestly and inconspicuously in the same library where his treasured books found place, but unfortunately the Nazi invasion of Italy has looted my books, and many precious documents I had collected. However, for many years I have worked in Cushing's library in constant contact with his personality, with his mind, with his vivid and always present guidance. The books which he collected are around me, as living witness of the work he accomplished. When I first came to Yale seven years ago, too late to find him alive, I was sorry to have no longer the opportunity of meeting him and having the privilege of his invaluable advice. But later working in the

rooms which bear his name and in which his treasures are collected, I felt that even so I was working under his auspices. There is a figure in Vesalius' *Fabrica* in which the meditating skeleton looks at the skull on a marble table which has the inscription "Vivitur ingenio, caetera mortis erunt, One shall live through his genius, all else will die." In the library Cushing's genius is alive. I have had the opportunity during my wandering life to work in almost all of the most famous libraries of the world, in the Marciana in Venice, in the Laurenziana in Florence, in the Vatican Library and in the Libraries of Paris and of Oxford. I have had the privilege of seeing and studying the most precious books which present the documentation of the history of human civilization. But Cushing's library is quite different from all the others. The great libraries have generally lost the mark of the personality of the people who bought and owned the books; they are collections of books just as a museum is a collection of works of art, exhibited for the admiration and for the study of the visitor and the name of the donor is listed by a label or an inscription. But Cushing's library is the library of a passionate bibliophile. He had not finished his task at the moment in which the book finally was in his hands. He began to study it, to be interested in the history of the author and of his life, of the people among whom he had lived, of his friends and his publishers, he tried to learn still more about the story of the book itself and of the previous owners, and he was so interested in the book and the content of it that he read it and studied it with the clear eyes of the researcher, with the acute criticism of the diagnostician who is searching for all details, for the places in which the author most clearly and exactly expresses his opinion, but at the same time for the peculiarity of an edition, for the misprints, for the errors in the numeration of pages or the indices. Maybe other people were able to do the same and did it. But we don't know anything about it, and we have not any proof of this peculiar form of passionate love for a book. Cushing was not only a man of genius, but also a practical worker, extremely diligent and exact. He was the type of a man of the Renaissance, the universal man, the researcher, the explorer and at the same time the lover of beauty; the perfect technician who cared for the exact details of the most minute part of his work. But also he was the great artist whose free mind and independent judgment was never definitely bound by any authority. He was, as a great artist of the Renaissance, convinced that there do not exist things of

little importance which may be neglected. The study of the book, of the bibliography, of the typographical characters, of the pages, of the binding had to be exact and correct, no less than the clever examination of the importance of the text. When you look at his drawings in which he was able to catch the character of a person or of a landscape with a few strokes, you understand his personality, just as when you attended any of his operations; he was always careful for the perfection of his technique and for the complete accomplishment of his program. Such were the great scientists and artists of the Renaissance like Benvenuto Cellini who gave to the smallest object which came from his workshop no less attention than he gave to Perseus.

In many books of Cushing's library you find some notes, often pages, written by himself in his fine writing or dictated to his secretary. These pages are a precious mine of information; they are, I believe, the personal introduction of the reader to the author by Harvey Cushing. There you find a discussion on the life of the author and on his activity, some important notice about the publisher and the printer and the time in which the book appeared; then information about the success of the book, the price it was sold for, the judgment of critics and of readers; finally, a series of small observations on differences between this one copy of the book and other copies in other libraries, on the rarity of the book; on the price for which Cushing had purchased it, from whom, where and under what conditions. In other pages you find a summary of the contents and a quotation of the most important passages. We can say that after reading Cushing's introduction, the book or the manuscript of the ancient author is no longer unknown to you, his work is not distant and inaccessible; on the contrary you have the feeling that somebody who is an expert has taken you by the hand showing you the way. You are encouraged and you proceed with the belief that you will be able to find surely and easily what you like.

Cushing's choice of books speaks eloquently for his education, for his taste, and for the universality of his interest. He collected medical books and was chiefly interested in Vesalius and the books on anatomy in the Renaissance, but besides that almost any chapter of medical history had an appeal to him; all books on magic, on astrology, on philosophy, and in general on every current of ideas directly or indirectly connected with medicine awakened his interest and his curiosity. One of the most precious books of the Cushing library is the famous Calendar by Johan-

nes Regiomontanus printed in Nuremberg by the private press of the author in 1474. It is one of the most beautiful, probably the most perfect copy extant of this book, surely better than the copy of the British Museum. It is the extremely rare *editio princeps* of the celebrated Calendar which was the prototype of all calendars in book form, and contains the astronomical tables and tables for calculating dates and festivals for 1475-1513. There are more than fifty wood cuts, illustrating eclipses of the moon and sun, and a chapter on the best time for blood-letting. In the book you find a notice of ten pages of information inserted by Cushing with the exact description of the book, with the story of its author, with the life of the man who owned the book, a certain Serlinger, Bishop of Sekkau, near Strassburg, and eventually the description of the tombstone of this Bishop. When you have read his learned introduction you are able to appreciate the importance of the book and the rôle that books of this type which are now extremely rare have played in the history of the culture of the middle ages.

On many occasions Cushing admitted the firm hold books had on him and he described book collecting as "Worse than the opium habit, but much more fun." He wrote also about it in his "Apologia" which is an introduction to the bio-bibliography of Vesalius: "The slowly progressive so rarely fatal malady, bibliomania, while commonly a masculine ailment, easily leads to difficulties because of an even more serious counter-disorder which is prone to affect the distaff members of the family, who usually control the majority vote. They show an uncontrollable tendency to accumulate odds and ends which mysteriously find their way, under the general name of antiques, into the house late in the day by way of the garage after all identification tags have been removed. On the other hand a new old-book unmistakable in its brown paper parcel and bearing unfamiliar foreign stamps is handed in openly at the front door by the postman, thereby advertising its arrival from parlor to kitchen. . . . Most collectors of books in self defense conceal them in their so-called dens, fully convinced that they have made a better investment for the long pull than has the party of the first part."

Speaking once at the dedication of the medical library in Cleveland he said: "I warn young people against book-collecting for one may easily become enslaved and soon so enveloped by books that they are on the floor and out in the front hall and in the dining room till you never can find the volume you want and feel sure your wife or the

children must have taken it from the place you last put it, when they borrowed your paste pot and scissors. . . . In fact beware of books; as a species they are imperishable and against their multiplication nature has no chance whatsoever. The time will come when every tree has been felled for paper, every calf for leather and the few-longhaired and undernourished people left in the world will be madly making card indices of the volumes which have filled every available cranny in which they can be stored. Yes, beware of books as an expensive habit and waster of time."

A very nice story characterizing the passionate book-collector was told by Cushing in the same oration. "A friend has been staying with me whose metabolism and pulse rate in the presence of other people's books run high. He grows exophthalmic with hyper-biblioism so while you endeavor to concentrate upon your task he exclaims: 'Where did you get this Dolet imprint?' holding up a vaguely remembered calf of a book in his hand. 'Oh I don't remember, someone may have left it at the door, but I always thought it came into being on the bottom shelf of that case in the corner.' 'Are you aware,' says he, ignoring my trivialities, 'that Christie knew of only one other copy?' You begin to take interest. 'Perhaps someone gave it to me for Christmas. But what about Dolet? Let me see the book; it's only just grown up.'

"And there it was, sure enough—*A Lyon. Chés Estienne Dolet, 1542. Avec priuileige pour dix ans.* And, what is more, with two other Dolet imprints, *Des Tumeurs* and Galen's *De la Raison de curer par Evacuation de Sang*, newly translated from the Latin into French by the printer—a veritable triplet.

"This is enough; you are lost. The attack is on. Influenza in its abruptness is nothing to it, and days elapse before you are fit to resume your legitimate job. Your fever leads you first to Richard Copley Christie's life of the unfortunate Etienne Dolet, the young Renaissance scholar and printer, . . . and then you are anxious to know about Christie. . . . Beware the book."

Harvey Cushing did not follow this humorous advice he gave to his audience; he loved the books; he followed the traces of the books, authors, their publisher and their printer. He liked to state, as far as possible, the influence which a book had on the current of thought of its time, the people who copied and plagiarized it, the enemies who attacked its author, the friends who defended him. He became a clever

historian of medicine who, starting from the details arrived at the main problems of medical history, just as an explorer who, taking his way from a hidden and unknown place, arrives through roads he never had passed before to the main road of human thought. He was therefore also able, as a book collector and as a great teacher, to inspire other people through his example and through his suggestion with a love for books and interest in historical studies.

Harvey Cushing is one of the many examples that we know of a scientist and an experimental researcher, of a surgeon and physiologist who never lost his fundamental character as a humanist. He was a humanist in the most noble sense of the word. He possessed the feeling of the cultural tradition of humanity intended as continuity in thinking and in learning humanism as a cult of beauty and a search for glory. Like Leonardo who was the great man of the Renaissance, no less a great scientist than a great poet, anatomist, mathematician and mechanic, Harvey Cushing was a complete personality and his work as book collector is only one interesting facet of his individuality. In this field all the outstanding qualities of his temperament and of his genius are expressed no less than in his work as physiologist and as surgeon. In this field as in all fields of his work the saying written on the marble on which Vesalius' skeleton is meditating is true; *Vivitur ingenio*; through his genius one may survive.

THE CAUSES OF CANCER

*The Annual James Ewing Memorial Lecture**

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I WISH to thank Dr. L'Esperance and the other members of the Committee for their invitation to deliver the Memorial Lecture in honor of Dr. James Ewing. Memories of many years past lead me back to my acquaintance with Dr. Ewing. Between the years from 1903 to 1910 when I was associated with the University of Pennsylvania, I had occasion to visit New York and to meet Dr. Ewing at various times. We were both interested in Cancer Research. Dr. Ewing at that time carried out among other studies investigations into the nature of the so-called infectious tumors of dogs. He was thus one of the early investigators in the field of Experimental Cancer Research; but from the beginning he was also greatly interested in the Pathology of human tumors and he produced later his authoritative book on "Neoplastic Diseases" in which he analyzed with a keen scientific spirit the principal data which are of importance to the pathologist and especially also to the physician. He has thus exerted a great influence on medical science, theoretical as well as applied, not only in this country but also in other countries wherever his work became known. He contributed original investigations especially concerning the nature of bone tumors, where one type bears his name. He combined thus in an outstanding manner an interest in and a profound knowledge of experimental cancer research and of the pathology of human tumors.

I cannot claim for myself the same universality of interest. My studies were concerned largely with the experimental growth of tissues and tumors and I have carried on research in this field for more than fifty years. I shall here endeavor to present a picture of the different directions in which cancer research has extended and of some of the

* Given May 1, 1947 at The New York Academy of Medicine.

trends of cancer research during this period and of what I consider the essential, though tentative conclusions that can be formulated at the present time.

THEORY OF CANCER

We shall first recall a theory which we stated in 1916 and which we had occasion to restate repeatedly since then. It may be formulated approximately as follows: Cancer develops if a combination of stimulating factors and of genetic factors makes possible a series of growth processes, which gain gradually in intensity. Intermediate steps in this continuous process of cancerization are represented by states of increasing sensitization, as a result of which specific stimuli no longer are needed for the tissue to reach the state of cancerous growth, but in which non-specific or less specific factors can accomplish it.

It has been assumed by some investigators in recent years that at the time when the tissues no longer needed specific stimuli for the completion of the process of cancerization, a transformation of some tissue cells into cancer cells had already occurred and that these cancer cells subsequently gave origin to the cancerous growth. However, there are several considerations which seem to make this interpretation less probable than the assumption that intermediate stages between normal tissue cells and typical cancer cells exist and that such intermediate tissues may react as would sensitized tissues.

The genetic hereditary factors seem to act in the process of cancerization, principally by making the tissues more responsive to growth stimuli. But even after the cancerous state has been reached, the process of stimulation does not necessarily cease; it may continue and intensify the cancerous change and increase the proliferative and invasive action of the cancer cells. Concomitantly with the continued stimulation of the tissue the chemical and morphological constitution of the cells is modified. The tissue thus becomes more and more independent of the action of the external growth stimuli of various kinds. As the result of this long continued activity of the external stimuli in coöperation with the genetic factors, there gradually develops a growth factor within the cell and presumably within the cytoplasm, which incites the cell to continuous growth. The cancerous change affects principally the organ and tissue differentials, which means those cell characteristics which differentiate the different tissues and organs within the same individual,

while they leave the characteristic which is common to all the organs and tissues within the same individual, strain or species, the individuality and species differentials, to a large extent unaltered. The inner growth factor which has been created has the power to propagate autocatalytically. Thus the cancerous condition has become permanent.

Although cancer differs from all other growth processes in very characteristic ways, yet the various factors which are the cause of all the other growth processes, such as hormonal and regenerative or embryonal growth, may also act as causes of cancerous growth, but only as partial causes which need to be supplemented by the action of genetic factors. They represent the stimulating factors, which ultimately lead to the production of the inner growth factors, provided the genetic constitution is favorable for such an effect.

GENERAL CHARACTERISTICS OF GROWTH STIMULI

In a general way we can divide growth stimuli into two classes: 1) Those which exert a direct stimulation of growth without first inflicting an injury on the cells. Growth hormones are an example of such factors, and 2) other factors which primarily cause a tissue injury which is followed by growth processes of a regenerative nature. Both of these classes may be active in the induction of cancer. There are probably conditions of an intermediate nature, in which external factors alter the cell equilibrium in an abnormal way and thus inflict injury, but in which the damage is not so great as to lead to visible pathological changes in the tissues.

STIMULATING FACTORS IN THE DEVELOPMENT OF CANCER

As stated, growth factors in general may function as stimulating agents in the formation of cancers. This effect of stimulating factors in the production of cancer does not, however, mean that all of these factors are equally effective in producing cancer or that in addition some special growth factors which do not play a role under ordinary conditions may not also be active. Such special factors do exist largely in the form of tar and of certain polycyclic hydrocarbons, but these also, as far as is known, seem essentially to represent growth inductors which do not in principle differ from all the other growth factors mentioned. Yet because they are not known to play a role under non-cancerous conditions, and because they are very effective as cancer

inductors, there has evolved in many investigators the implied or openly expressed conviction that these hydrocarbons are the real, though hidden causes of cancer which are active when cancer arises apparently spontaneously without any known efficient cause. As far as it can be determined these cancer producing hydrocarbons act as direct growth stimulators and do not call forth a primary injury which would then be followed by proliferation. It is very probable that they are so effective as cancerigenic agents, because they are so effective as growth stimulators of tissues. Of special interest in addition to the cancerigenic hydrocarbons are certain azodyes, such as p-dimethylaminoazobenzene, o-aminoazotoluene, and substances such as carbon tetrachloride and chloroform which produce malignant tumors in the liver of rats and mice when fed by mouth or after parenteral administration. In all probability they cause primarily injury of the liver cells either directly or in association with deficient diets and these effects are followed by regenerative and compensatory growth processes which by way of adenoma step by step pass into malignant cholangioma and hepatoma. Whereas ordinarily under-nutrition tends to delay or prevent cancerous growth in the case of these tumors dietary deficiencies of a certain kind by causing tissue injury, may lead to the formation of cancer. These and various other problems have been studied in this country especially by Rhoads, Kensler, Dobriner and Sugiura, Chambers; by Miller, Baumann and Rusch and by Andervont, White, Edwards and Eschenbrenner and by Opie.

HORMONES AS STIMULATING FACTORS

Before the effectiveness of these two types of substances in the production of cancer had been discovered, it was found in 1915 and the following years that hormones and above all others sex hormones may act as potent agents in the production of spontaneous cancers. They are the only cancerigenic substances known so far which are normal constituents of the animal body and which here exert a normal function mainly and primarily as growth stimulators in the accessory sex organs, and as a result of this function, may cause the development of cancer in the organs in which they normally induce growth processes. They also control here various metabolic activities and secondarily they affect certain other organs. They do not as a rule act locally at the site of injection, except in the organs to which they have a specific affinity;

nor is their chemical constitution as such of importance; the essential condition is that wherever applied, they induce proliferation in specific organs and in these they induce cancerous changes; therein, as well as in some other respects, they differ from the cancerigenic hydrocarbons. But hormones and cancerigenic hydrocarbons and also azodyes resemble one another in that they all act in coöperation with genetic factors. While the cancer producing action of hormones is exemplified so far by the sex hormones and especially by estrogen in its action on mammary gland, vagina and cervix, and also on the interstitial gland of the testicle, as Bonser and Gardner have observed, and on the anterior hypophysis, it could be predicted in the beginning of our investigations that presumably other hormones might exert corresponding effects: More recently it has been observed by Woolley and Little that also adrenal cortical hormones may exert a cancerigenic action and by Bielchowsky that thiourea acting in a hormone-like manner on the thyroid gland may, in coöperation with aminofluorene, induce tumor formation in the thyroid gland.

As far as is known at present in every case of experimental cancer induction under the influence of hormones and of cancerigenic hydrocarbons, a period of sensitization precedes the cancerous end process; moreover cancer is not caused by the action of the hormones on single cells of the recipient organ, but on the structural organ units, and the same fact applies to the action of some other cancerigenic agents. But in contrast to certain other cancer producing factors hormones induce these growth processes and thereby cancer not by means of primary tissue injury, which would be followed by secondary regenerative proliferation, but by a direct stimulating action on the tissue substratum.

Clinical observation has shown the importance of tissue injury as one of the causes of cancer. In experimental cancer, trauma has been established as one of the coöperative causes of cancer in the case of cancer of vagina and cervix and of the epidermis in mice. In both the clinical and the experimental cancers the tissue injury must be long continued or often repeated, it must be chronic, in order to be effective.

X-rays, gamma rays and ultraviolet light may act as cancer inducers in tissues which are able to absorb these radiations. They seem primarily to cause tissue injury, in addition to mutations which they may induce in germ cells. However there exists after all the possibility that these radiations may also be able to induce primary growth by way

of direct tissue stimulation. This is conceivable because there are strong indications that tissues at a certain stage may become actively immunized against these injurious actions, and that thus the injurious actions are mitigated. In this connection the observations of Furth on the production of ovarian granulosa cell tumors in mice by the action of X-rays in certain strains of mice may be of special interest; it may perhaps be possible to determine whether these tumors may not develop without a preceding injurious action of the X-rays on the tissue substratum.

Cancer may be caused by metazoic parasites. It appears most likely that directly or indirectly, as the result of the activity of these parasites, substances are produced which stimulate the surrounding tissue to grow and to become cancerous. Although no definite demonstration of the existence of such substances has been given so far, the recent experiments of Dunning and Curtis suggest that substances or agents present in the parasites may be responsible for the cancerous change.

As to the mode of action of these various stimulating factors, they seem to have in common the characteristic that through successive stimulations they initiate growth processes which occur in certain rhythms and that each stimulation at least tends to be followed by a return of the affected tissue to its original state; the processes induced by the stimuli would then approximately be cyclic. But such a return to the normal condition is not complete and therefore an accumulation of successive growth stimulations will take place and in the end this will lead to the production of cancer. The cancerous transformation resulting from the accumulation of successive growth stimulations would take place by way of an intermediate state of tissue sensitization.

GENETIC FACTORS IN THE ORIGIN OF CANCER

The various stimulating agents which we have discussed so far can produce cancer only if they have a chance to act on a tissue substratum which is able to respond to such stimulations with growth processes of a certain intensity. The mode of response of the tissue is dependent largely on genetic factors, which latter determine the constitution of the reacting tissue. It has been found that on the whole the tendency to cancer formation of different organs differs greatly within the same individual; and that these differences are characteristic of the species

and especially of the individual and of the strain to which the individual belongs, provided the strain has been made relatively pure through close inbreeding. However, a completely pure strain does not exist, as transplantation experiments between individuals which are members of such a strain have shown. It seems that in each individual a slight remnant of its own individuality differential persists through many generations of brother to sister matings. As stated, different organs of the same strain or individual differ greatly in their tendency to develop cancer and this tendency in one organ of an individual seems to be independent of that in another organ of the same individual. These tendencies are therefore determined mainly by the genetic constitution of the various organ and tissue differentials, and they are a part of the mosaic genetic constitution of the individual.

There are valid reasons for assuming that multiple genetic factors are concerned in the origin of cancer and that furthermore in general a quantitative relation seems to exist between the strength of the stimulating factors (S) and of the genetic hereditary factors (H) in the production of cancer (C) which can be approximately expressed by the equation $H \times S = C$. The stronger the genetic factors are, the less strong do the exogenous stimulating factors need to be, and vice versa, in order to accomplish the cancerous transformation. In certain cancers which develop on an embryonic basis, the sensitization of the tissues involved seems to be so great that apparently non-specific factors may induce the development of cancer. According to the recent investigations of L. C. Strong it seems also that in a number of substrains of mouse strains N H and N H O, it is principally the genetic factors which determine the development of cancer in various organs; and different organs seem to exhibit this tendency in different kinds of these substrains, which latter owe their origin to germinal mutations. In the main these tumors behaved in a similar way to those that develop on an embryonic basis. In both conditions it appears as though we had to deal with sensitized tissues which no longer needed specific stimulating factors for the induction of tumors.

Besides these types of cancer which seem to be predominantly inherent in the constitution of the tissues there are others which are caused largely by the action of external conditions and in which genetic factors are of minor importance owing to the great intensity with which such external factors act. For instance, in the case of long con-

tinued application of X-rays to the unprotected human skin, it seems that cancer develops in almost all individuals irrespective of their genetic constitution.

As to the mode of action of the genetic factors, they may in some cases exert their effects indirectly through initiation of other predisposing factors; thus, for instance, certain diseases which develop partly on a genetic basis may promote the subsequent development of cancer; but as a rule genetic factors act by affecting the degree of responsiveness of the organ subjected to specific growth stimulating factors. According to Little and to Heston, Deringer and Andervont in the case of the carcinoma of the mammary gland in mice, also the propagation of the milk factor which may coöperate with hormones in the development of this tumor seems to be controlled by genetic factors; those genetic factors which cause a high degree of responsiveness of the mammary gland to stimulation by hormones also promote the propagation of the milk factor.

It is especially those investigators whose interest has centered mainly in the genetic hereditary factors in cancer and those who have studied the nuclear and chromosomal changes taking place in tumor cells or in tissue cells, during or preceding their transformation into cancer, who, on the whole, have favored the theory of mutations in tissue cells, somatic mutations, as the essential cause of cancer. However, there are several considerations which make this interpretation very improbable and we may conclude that somatic mutations due to changes in genes and chromosomes are in all probability not concerned in the origin of malignant tumors. This conclusion applies only to somatic mutations and not to germinal mutations—mutations in the genes or chromosomes of the germ cells. It is very well conceivable and even probable that germinal mutations are involved in cancer development; that they may determine the degree of responsiveness and sensitization of a certain organ or tissue to growth stimuli of various degrees of specificity and intensity and that in some instances the responsiveness may become so great that the ordinary metabolic and mechanical changes concerned in the process of living are sufficient in the end to induce cancer formation. In this case endogenous genetic, inheritable factors as such may be able to induce development of cancer and specific extraneous stimuli apparently are not needed. For instance there seems no reason for assuming that ovarian hormones produce the usual series of changes in

the mammary gland, cervix and vagina, namely first ordinary growth, then hypertrophy to be followed by adenoma and in the end cancer by means of somatic mutations. However, these objections to the application of the term "somatic mutation" hold good only, if we use this term in the strict genetic sense. If we extend the definition so as to include not only changes in genes and chromosomes but also a series of steadily increasing cytoplasmic changes, then the origin of cancer may be attributed to somatic mutations, and we also have formerly used this term in this wider sense. But before doing so, there should be a clear understanding as to the manner in which this term is defined. The conclusion that somatic mutations in the strict genetic sense in all probability are not the essential cause of cancer carries with it the implication that also cytoplasmic factors, and not solely nuclear factors, may be involved in the development of cancer. In favor of the importance of cytoplasmic factors, there may be cited, besides some older observations concerning the propagation of certain cytoplasmic cell constituents, the recent observations of Sonneborn in *Paramecia aurelia* and of the Lindegrens and Spiegelman in *Saccharomyces*. Both of these sets of observations agree in regard to the importance of cytoplasmic factors in the hereditary transmission of cellular characteristics and also in the origin of these factors from the nucleus. As far as the development of cancer is concerned, these investigations lend support to the view that also in this case cytoplasmic factors may play a significant role.

THE INTERPRETATION OF THESE DATA

The multiplicity of external causes of cancer which have been observed led some investigators to look for one underlying common factor to which all the others were subordinated. It was especially Borrel, who in the early part of this century upheld the view that this common factor consisted in a virus, which was carried to a tissue with the help of the various other factors mentioned, which latter were thus of a subsidiary nature. On the other hand we expressed the view that the common underlying conditions present in these various stimulations were the long continued and gradually intensified growth processes which were induced in the tissue substratum and we furthermore found evidence for the conclusion that by way of tissue sensitization these growth processes as such, or processes intimately connected with them, led in the end to the cancerous transformation of the normal tissue. As

stated, the increased growth and also motility of the tissues exhibited under these conditions were attributed by us to the production of an intracellular growth substance, which propagated within the cells autocatalytically, and the automatically continued production of this substance was considered responsible for the irreversible character of cancer. We thus distinguished between multiple exogenous growth factors (eg) which coöperated with genetic factors and the autocatalytically propagating inner growth factor which resulted from this co-operation. It was also suggested at that time that under certain conditions such an autocatalytically propagating growth substance might be separable from the tissues; it might then be experimentally transmitted to related hosts and here induce cancerous changes. This growth substance (ig) might thus act like a virus, although it was of endogenous tissue origin. We believe it very probable that the concept of autocatalytically propagating growth substances of endogenous derivation applies to the large majority of tumors in animals, including man. As pointed out by us somewhat later there exists in addition under certain conditions an analogy between the action of cancer producing stimulating factors and the action of organizers or inductors in embryonal development, where through contact action they transform one kind of tissue into another.

When it was found that one type of pneumococci can be transformed into another type under the influence of a substance present in the second type, Murphy compared such mutagenic substances with the action of avian sarcoma agents which transform normal cells into sarcoma cells. A further similarity between the avian sarcoma agents and the substances which change types of pneumococci consists in the fact that according to Avery the transforming substance in pneumococci is a nucleic acid and that viruses also consist of nucleic acid-protein combinations with or without the association with lipids. However whereas the type-changes in pneumococci take place suddenly and rapidly, the cancerous transformation of normal tissue cells into cancerous cells takes place step by step and requires as a rule a long period of time. The usually rapid action of the avian sarcoma agent seems to be an exception to this rule; we have already referred to the possible interpretation of this effect and we shall discuss it again in another connection. These observations lead us to a consideration of

VIRUSES AS CANCER AGENTS.

The essential data in this field we owe to the investigations of Peyton Rous and his associates, especially Beard, Kidd and Friedewald, and subsequently other investigators have made important contributions. In four types of cancer, viruses or agents resembling viruses may play a part in the induction of the cancerous growth: 1) In certain cases of fowl sarcoma it has been found by Peyton Rous and also by Fujinami that in some tumors filterable agents can be separated from the tumor cells. 2) The benign papillomatous tumors discovered by Shope, in cotton tail rabbits, can be induced by a virus and under certain conditions can change into carcinoma. 3) The mammary carcinoma of the mouse in which a virus-like substance, discovered by Bittner and present as a rule in the milk and in some organs of mice, belonging to high mammary tumor rate strains, may play an important role in the carcinomatous transformation of the mammary gland tissue. 4) There are indications that adenocarcinoma of the kidney in *Rana pipiens* may be caused by a virus (Lucké).

The agents of avian sarcomas are situated in the tumor cells; they are filterable through filters that retain the cells. In very young chickens in which the resistance to the virus is as yet very slight, the latter may give rise to generalized hemorrhagic lesions instead of to tumors (Duran-Reynals). In an adult chicken which bears such a sarcoma antibodies may develop against this tumor. As Rous has found the sarcoma virus tends to fix itself to growing tissue and according to Murphy it is absorbed specifically by muscle of fowl in contradistinction to muscle of other species, and herein as well as in certain other respects it shows fowl-specific characteristics.

Beginning with the experiments of Murphy and Landsteiner attempts have been made by various investigators to determine whether or not in chickens, in which a sarcoma has been produced by injection of tar or carcinogenic hydrocarbons, the presence of a sarcoma virus can be demonstrated. It seems that in a few experiments of McIntosh and Selbie such a virus has been found. However the large majority of such experiments, especially those of Murphy and Peacock, were negative, and it is very probable that as a rule avian sarcomas which are induced by cancerigenic hydrocarbons do not contain a virus.

As to the mode of origin and nature of these tumor-producing vi-

ruses, no definite statement can be made.

1) *The virus of rabbit papilloma.* Shope discovered in the papilloma of the skin of cotton tail rabbits a virus which can be transmitted to the epidermis of the domestic rabbit and here also give rise to papilloma formation. In the latter species the papilloma may in the course of time become transformed into squamous cell carcinoma, in which as a rule the virus can no longer be demonstrated by inoculation experiments. However, antibodies against the Shope virus may form in such rabbits. The relation existing between the papilloma and the carcinoma developing from the former have been studied mainly by Rous and his collaborators, Kidd, Beard, Friedewald and McKenzie. They observed that a papilloma, which developed in domestic rabbits following inoculation of the papilloma virus, can be changed into carcinoma by application of tar, and conversely that a tar papilloma in a rabbit can be rapidly transformed into a carcinoma by intravenous injection of papilloma virus. Both of these agents, tar and virus, seem therefore to act in principle in a similar manner.

2) *The milk agent.* The agent present as a rule in the mammary gland of mice, belonging to high mammary tumor strains, is transmitted with the milk of the mother to the young (Bittner) and then may coöperate with genetic factors and with hormones in the production of mammary carcinoma. But in order to be effective the milk factor has to act on the mammary gland of the mouse at an early age. It seems to fix itself on the mammary gland tissue and it helps to accelerate growth processes which ultimately lead to cancer formation. However, under the influence of carcinogenic hydrocarbons mammary carcinomata may develop without the coöperation of the milk factor. These tumors are essentially like those which develop under the influence of ovarian hormones; differences which exist are merely of a quantitative nature. It seems moreover that also under the influence of ovarian hormones, in particular estrogen, mammary carcinoma can develop without the coöperation of the milk agent. Carcinomas of vagina and cervix, as well as all other types of cancer which are produced by estrogens or other stimulating agents, are not apparently influenced by the milk factor, although in leukemia it may perhaps have a very slight effect, not identical with that exerted in mammary carcinoma (Furth), nor has it so far been shown that the milk factor is active in any species other than the mouse. All these facts do not favor the interpretation

that the milk factor is the real "inciter" of mammary carcinoma in the sense in which the avian carcinoma agent is the cause of fowl sarcoma, and that the ovarian hormones are only of secondary importance. On the contrary all data point to the conclusion that the ovarian hormones represent the essential stimulator of mammary carcinoma as well as of certain other tumors, especially those of the accessory female sex organs and those of the pituitary and of the interstitial gland of the testicle, and that the milk factor acts as a subsidiary growth factor in the production of mammary carcinoma of mice.

The mode of action and significance of viruses in the production of cancer. The findings concerning the production of certain cancers by means of viruses suggested to Rous, Andrewes and others, the theory that viruses may be involved in and be the immediate cause of all types of cancer and that all the other known cancerigenic factors are merely of secondary importance, enabling the viruses to fix themselves on tissue cells and perhaps inducing them to undergo mutations, thus rendering them cancerigenic. Such a concept presupposes that viruses are present, though in an inactive state, in all organs and tissues of organisms liable to become cancerous, including embryonic organs. This conclusion rests on the assumption that cancer-inducing viruses are tissue and organ specific. This seems to be largely true, although to a limited extent such viruses may apparently act on more than one type of tissue. The necessity for assuming the constant presence of distinct viruses in so many different organs and tissues of each individual has suggested more recently to Altenburg the view that viruses may have invaded all the tissues of higher organisms in earlier phylogenetic periods and that since then they continue to inhabit these organs as symbionts (viroids). This hypothesis would then imply the interpretation that endogenous autocatalytic growth substances causing the production of cancer were originally extraneous organisms which as symbionts had become adapted to the host cells.

However, there must be considered at least two distinct modes of action of the cancer-producing viruses which are known so far. The agents of avian sarcoma seem to accomplish the cancerous transformation directly and rapidly through invasion of a specific tissue, especially one undergoing temporary growth processes. As far as the invaded cells are concerned, all they need in order to become cancerous is to accept the virus. Yet, it has been found that, as the result of the invasion by

viruses, these cells have acquired new metabolic characteristics which distinguish cancerous tissues from normal ones. On the other hand, the virus of rabbit papilloma and likewise the milk factor seem to act by inducing growth processes in the normal tissues which are gradually intensified and in coöperation with other factors in the end lead to their entering the carcinomatous state. These viruses behave therefore essentially like the other stimulating factors or they may act by intensifying the response of normal tissues to other stimulating factors. They lead to active metabolic and other changes in the tissues and thus also to proliferative processes which end in the transformation of these cells into cancer. However, as stated, also the fowl sarcoma agent seems to induce active changes in the cells it has invaded, and, moreover, in some instances, it apparently requires a longer time in order to accomplish the cancerous transformation of the mesenchymal cell. The difference in the cancerigenic action of these two types of viruses may therefore after all not be of a radical nature.

When it was found that cancerigenic viruses cannot as a rule be demonstrated in mammalian cancers—and the recent experiments of Woglom confirm this conclusion—the attempt was made to demonstrate their presence by immunological methods. It is probably this aim, based on the conception that a virus is the immediate cause of every type of cancer, that gave rise to the immunological studies of Kidd. In these experiments Kidd analyzed the nature of the antibodies which develop in rabbits implanted with the Brown-Pearce rabbit carcinoma. He found that two types of antibodies develop: 1) one which is specific for the antigen of the Brown-Pearce tumor cells, and 2) one which reacts also with normal rabbit tissues; there exists in addition 3) a natural antibody which is present even in rabbits which have not been implanted with Brown-Pearce tumor and which reacts with the cancer cells as well as with normal rabbit tissue. Also another rabbit carcinoma V₂ which had originally developed from a Shope rabbit papilloma was found to possess an antigen which could give rise to the production of a specific antibody and which differed from the antibody directed against the Brown-Pearce tumor. Because these specific antibodies reacted also with Claude's microsome fraction of the tumor cells and furthermore because there was no indication of the presence of a virus in either of these two tumors, Kidd inclines to the conclusion that in both of these cases a cell constituent, rather than a true virus, acted as antigen and

that this antigen may perhaps have functioned in a way similar to the autocatalytic intracellular growth substance which according to the theory discussed already, is supposed to be the immediate direct cause of carcinomatous growth. These experiments of Kidd then support the view that it is not likely that true viruses are responsible for the origin of the large majority of mammalian cancers, although in certain instances there is a probability that such viruses may be involved. Also the recent experiments of Rous and Smith, in which they succeeded in producing cancer in two different embryonic organs, through direct application of methylcholanthrene to transplanted embryonic material, taken together with some supplementary experiments, are unfavorable to the view that viruses must be the cause of such cancers and therefore of mammalian cancers in general. Yet in addition to the conditions already mentioned there are some other conditions in cancer development which might leave open both possibilities, namely, that either true viruses are involved or that autocatalytically propagating growth substances are the essential cause. Conditions of this kind are: 1) The long known fact that in the course of serial transplantation of tumors as a rule an increase in growth energy of the transplanted cells takes place. Is this due to the stimulating effect which the process of transplantation exerts on one of the cell constituents or is it due to a change which takes place, as a result of the transplantation, in a virus previously introduced into the cell from the outside? 2) The observations, likewise dating back a long time, that the growth of carcinomatous epithelium may induce a sarcomatous transformation in the adjoining stroma. Is this due to an organizer like action emanating from the carcinoma cells or to the transfer of a virus from the epithelium to the connective tissue? 3) The experiments of Taylor and his associates in which carcinomatous tissue was cultivated in the yolk of chicken eggs. Injection of cell free filtrates of such yolk into mice seemed to be followed in certain cases by the development of sarcoma. 4) Experiments by Silver in which cell free filtrates from mouse sarcoma in its early stages of development—a tumor induced by 1, 2, 5, 6—dibenzanthracene—after injection into other mice, gave rise to sarcoma formation. Likewise in recent experiments of Herly transfer of ascitic fluid, produced in the peritoneal cavity of mice through the injection of methylcholanthrene, to the peritoneum of other mice could under certain conditions give origin to sarcoma formation. 5) According to A. Fischer repeated auto-

transplantation of normal mammary gland tissue may result in carcinomatous changes in the transplant and Earle observed that after long continued growth of mouse fibroblasts in tissue culture their transplantation back into the mouse led to the development of sarcoma. This occurred after serial transfers in heterogenous media and with addition of small amounts of methylcholanthrene, or perhaps even without such an addition. Earle considered therefore the possibility that fibroblasts may be able to undergo these changes by growing in tissue culture in heterogenous media without the action of cancerigenic hydrocarbons. Gey from similar experiments concluded that the action of methylcholanthrene is not required in order to obtain such a sarcomatous transformation. Do we have in these experiments to deal solely with the effect of long continued growth processes which take place under special conditions and which lead to the production of the autocatalytic growth substances in the fibroblasts, or is the addition of methylcholanthrene at least in part responsible for the results? Or are real viruses involved? Recent experiments of Sinai and Rifkind raise similar questions and they believe that they have obtained tumors after transplantation of apparently normal tissue under certain special conditions. The solution of these and various other problems must be left to future investigations and they may make more definite the line of demarcation between tumors in which true viruses are involved and those tumors which are caused by autocatalytically propagating, intracellular growth substances. However in giving due consideration to the experiments mentioned which need further investigation, there are a number of facts which make the view that extraneous viruses are the general immediate cause of cancer improbable. They are as follows: 1) In the majority of the mammalian and even of avian cancers it has been found impossible to demonstrate the presence of a virus. 2) The origin of such agents as those active in avian sarcoma and of the milk factor is unknown. 3) Effective cancer-producing agents such as hormones and certain polycyclic hydrocarbons and some other organic compounds are by themselves able gradually to push forward the growth activity of the tissue on which they act to such a point that the tissue becomes sensitized and at last becomes cancerous; even then the stimulation may not cease but by continuous action may intensify the cancerous state. It should again be emphasized in this connection that it is not sufficient for tissues to be for a short time in a state of active growth, in order

to become cancerous, but that a progressive concerted tissue growth, extending over a considerable period of time and caused and directed by the quantitatively coördinated action of extraneous stimulating and inherent genetic factors, must precede the development of cancer.

4) The stimulating substances seem to accomplish these effects not by transforming individual cells, as might be expected, if a virus acted on a tissue, or if a somatic mutation occurred, but it is a tissue unit as a whole which is thus affected and which in the end undergoes the cancerous change. 5) All those factors which inhibit or promote these growth processes influence in a corresponding way the development of cancer. Thus antagonistic hormone actions, general growth inhibitors, undernourishment tend to inhibit each in its own way the process of cancerization. 6) The more apt a tissue is to grow, the more readily it can be converted into cancer, a fact which applies also to embryonic tissues. This is borne out among others by the recent experiments of Greene and of Smith and Rous which indicate the great responsiveness of embryonic tissue to growth stimuli and its ready conversion into cancerous tissue, provided the genetic factors are suitable for such an effect. 7) Mention should also be made of one of the difficulties that might have to be faced if the milk factor were to be considered a true virus, whose function it is to transform the normal into cancerous mammary gland tissue. It would then be necessary to assume that the mammary gland tissues react to a virus of a different kind in those cases in which mammary cancer is induced without the coöperation of the milk agent and that this second virus would have to take over the function usually assigned to the milk factor. 8) The fact that Shope papilloma virus and milk factor act in the production of cancer not unlike certain chemical substances, which stimulate tissues to grow, or like hormones which induce proliferative processes, suggests that in other cases such chemical substances by themselves might be able to induce cancer formation.

We conclude then although in view of as yet existing uncertainties, only with certain reservations that the theory of autocatalytically active growth promoters which are derived from constituents of the tissue cells and originate in the course of the transformation of the normal cells into cancerous cells appears best to explain the development of the large majority of all cancers.

DISEASES OF THE COLLAGEN SYSTEM*

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THE term *collagen system* implies that the fiber-forming connective tissues which are distributed throughout the body represent an organic whole united by identity of basic texture as well as by similarity of function. Connective tissue is composed of cells and intercellular substance; the latter consists of fibers and a homogeneous ground substance. Upon boiling with water connective tissue yields a colloidal solution of animal glue or gelatin. For this reason the term collagenous tissue is used as a synonym for connective tissue. However, since collagen is derived entirely from the intercellular component of connective tissue, the designation collagen tissue places emphasis upon the intercellular substances. Thus the term collagen system points to the structural and chemical unity of these constituents of the connective tissue.

The term connective tissue connotes only the mechanical function of this bodily material. Yet other functions such as water and salt balance and the transference of metabolites from the blood to the parenchymal cells can also be attributed to it. The supportive functions evidently depend upon the tensile strength of the connective tissue fibers, while the colloidal nature of the ground substance makes it eminently suitable for the performance of metabolic functions. Again it is the extracellular portion of the connective tissue which presents a unity of action and thus justifies the term collagen system.

By providing a framework for the specialized parenchymatous cells, connective tissue plays an important role in the construction of all organs. In addition, in many organs it forms distinctive masses, such as the heart valves, which are structurally and functionally essential. Abnormal states of the connective tissue in such sites will obviously be reflected in morbid manifestations of the organs affected. Since our medical and especially our diagnostic notions have been expressed mainly

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in terms of organ pathology, morbid states of the collagen system have been interpreted as diseases of those organs which are most prominently implicated.

A review of the various concepts of disseminated lupus erythematosus and of generalized scleroderma will illustrate the gradual progress of our anatomic and pathologic comprehension of diseases of the collagen system; the history of rheumatic fever could serve equally well as an illustration. Both lupus erythematosus and scleroderma were originally regarded as diseases of the integument. The intense local and constitutional symptoms in disseminated lupus were recognized by Kaposi¹ as fundamentally different from those of localized lupus erythematosus. As early as the beginning of the present century Jadassohn² referred to disseminated lupus erythematosus as a constitutional disease. He stressed the occurrence of joint symptoms, mucosal alterations, glandular swelling, and especially renal complications. While these and subsequent clinical observations pointed to an involvement of internal organs, anatomical investigations disclosed no characteristic alterations other than those in the skin. Libman and Sacks³ first called attention to conspicuous involvement of the endocardium; subsequently Gross⁴ amplified these observations. Baehr, Schiffrin and I⁵ observed characteristic alterations of blood vessels, especially in the kidneys. These histologic findings were confirmed by the investigations of Jarcho,⁶ Denzer and Blumenthal,⁷ and Ginzler and Fox.⁸ The latter authors added necrotic foci in lymph nodes to the anatomical picture of disseminated lupus erythematosus. Libman and Sacks,³ and Gross⁴ defined the clinical syndrome of disseminated lupus erythematosus anatomically as a characteristic form of endocarditis. Baehr, Schiffrin and I⁵ in attempting to unify the histologic alterations observed in the heart, blood vessels and serous membranes, considered a primary endothelial alteration as the basic lesion. Keil⁹ expressed a similar point of view in his vascular concept of lupus erythematosus.

In 1941 further investigations¹⁰ caused us to reinterpret our anatomic observations. In these studies our attention was attracted to a striking alteration of the collagen tissue of the pericardium and myocardium. This change consisted of fibrinoid transformation of the fibers and swelling of the ground substance.

Minute study of the endocardium, blood vessels, serous membranes, skin, dispersed connective tissues of the mediastinum, retroperitoneum

and of the joint capsules disclosed identical lesions. In the spleen the collagen fibers in the adventitia of the central arteries were concentrically thickened. In lymph nodes the necrosis already described by Ginzler and Fox was traced to an alteration of the reticulum fibers. The ubiquitous occurrence of striking collagen alteration and its almost unique expression in the renal glomeruli and splenic arterioles seemed to us characteristic enough to serve as anatomic definition. Consequently we submitted the thesis that alteration of the collagenous system is the basic anatomic manifestation of disseminated lupus erythematosus.

We were aware that acute rheumatic fever is also distinguished by systemic involvement of collagenous tissue but we believed that the association of the specific Aschoff nodule with fibrinoid collagen changes and the absence of the characteristic renal and splenic lesions were sufficient to separate anatomically these two diseases which seemed also to be different on clinical grounds. Due consideration was likewise given to the presence of fibrinoid collagen alteration in periarteritis nodosa. The association with striking eosinophilic leukocytic infiltration, the prominent localization in the vessel wall and the far less conspicuous collagen changes at other sites were regarded as a cogent reason against identification of the anatomic lesions in disseminated lupus erythematosus and periarteritis nodosa.

Early histologic investigation of generalized scleroderma disclosed the characteristic thickening and homogenization of the collagen tissue in the corium. Similar sclerosis was soon observed within the vessels of the skin and in internal organs. Subsequently it was observed that the alimentary tract, lungs and skeletal muscle may also participate in this sclerosing process which obviously exerted its preponderant effect in the connective tissue framework of the organs. In association with this progressive sclerotic transformation of the collagenous tissue, fibrinoid alterations were observed by several authors, Masugi and Yä,¹¹ Pollack,¹² which showed some similarity in extent and localization with those occurring in disseminated lupus erythematosus. Conversely, since sclerosing collagen alterations were observed in the spleen in lupus a parallelism in the anatomic manifestations of both diseases could be inferred. However, it seems that the clinical dissimilarity of the two maladies should discourage any attempt to declare them identical. Indeed, the histologic features merely point to the possibility that the fibrinoid and sclerosing changes are different phases of a disturbed chemico-physical

state of the collagen tissue which has not yet been adequately defined. But the morphologic evidence certainly permits the conclusion that generalized scleroderma should also be included among the diseases characterized anatomically by implication of the collagen system.

By the use of the term diseases of the collagen system we wanted merely to call attention to the basic alteration found on histologic examination in certain maladies such as lupus erythematosus and scleroderma. We did not wish to assert that these diseases were thereby defined in an adequate manner.

Pathology aims at a full disclosure of the nature and causes of disease. The aim is slowly approached by a rational analysis of all the morbid manifestations. Alteration of organ and tissue structure, although an essential phenomenon of disease, is not the disease itself. Anatomic pathology perceives structure only. It proceeds from observation and description to a comparison of the morbid with the normal and thus establishes the criteria of structural abnormality. By trying to account for the development of deviations in texture it becomes morphologic pathology. Goethe refers to morphology as the science concerned with formation and transformation of living organisms. It is the ultimate object of medical investigation to establish the causal relation between the impact of external forces upon the human body and the manifestation of disease. By correlating altered structure with associated changes in the internal or external environment pathology enters upon the search for the reason of disease. But a multitude of factors is disclosed by searching clinical and laboratory observation. To select the essential factors requires acute discrimination and careful experimentation. The present state of opinion regarding the cause of diseases of the collagenous system illustrates the intricacy of an inquiry into pathogenesis. Indefinite toxins as well as specific bacteria, such as the tubercle bacillus, have been alleged as the cause of disseminated lupus erythematosus; but these notions have generally been abandoned.

Allergy was originally suggested as the etiologic factor in lupus erythematosus because of clinical considerations. The hypothesis has found support (Fox,¹³ Teilum¹⁴) since the characteristic alteration of fibrinoid degeneration of collagen tissue has been recognized in this disease. Similar changes observed in scleroderma have led Masugi¹¹ and other pathologists to assume that this disease likewise is of allergic origin. The hypothesis which regards fibrinoid degeneration as allergic tissue

reaction is derived from the experimental observations of Gerlach¹⁵ and Klinge¹⁶ and from the deduction of Gruber¹⁷ that the vascular necrosis in periarteritis nodosa is evidence of hyperergic inflammation. Subsequent investigations of Klinge¹⁸ and his associates and of Rössle¹⁹ have culminated in the belief that any disease characterized by fibrinoid change is presumably of allergic origin.

In recent years Rich²⁰ has strongly supported this view. It cannot be denied that fibrinoid collagen alteration is a feature of local anaphylaxis as seen in the Arthus phenomenon. Clinical and experimental observations strongly support the belief that periarteritis nodosa is of allergic origin. At the present time the allergic hypothesis in rheumatic fever deserves more recognition than any of the other explanations, such as specific organisms or dietary deficiency. Yet we must not lose sight of the fact that collagen alterations identical with or hardly distinguishable from those seen in allergy can be produced experimentally by various factors. Thus Tsai Tung Wu²¹ showed that simple squeezing of the skin results in fibrinoid degeneration; Schosnig²² observed fibrinoid collagen change in various acute bacterial infections. Fibrinoid alterations of coronary vessels have been seen by Meessen²³ in orthostatic collapse in rabbits. In experimental hypertension conspicuous vascular lesions simulating periarteritis nodosa have been reported repeatedly by Friedman et al²⁴ Smith et al,²⁵ Selye and Pentz.²⁶ Moreover the alteration which is found in collagen fibers in the base of a chronic peptic ulcer or in the vicinity of acute pancreatic necrosis is strikingly similar to fibrinoid collagen changes. Since such changes can hardly be attributed to an allergic factor, the conclusion seems justified that fibrinoid collagen alteration must not be interpreted solely and invariably as an expression of allergic reaction. This point of view, presented by us in 1942,²⁷ has been recently re-emphasized by Baehr and Pollack in a discussion of the lesions of disseminated lupus erythematosus and scleroderma.

Morphologic investigations of tissue changes in disease must aim at full comprehension of the physical and chemical factors responsible for the abnormal microscopic appearances. This goal of anatomic pathology is still far from being attained. Fibrinoid collagen alteration in particular demands searching analysis. Even the structure of normal collagenous tissue is still very incompletely understood and investigations of its chemical and physical constitution must precede an inquiry into its ab-

normal states. Investigations of the connective tissue fibers with the aid of the electron microscope and of x-ray diffraction have brought forward important information regarding its molecular structure. The nature of the homogeneous ground substance, its relation to the fibroblasts and to the collagenous fibers still awaits elucidation. Fragmentary observations suggest that the ground substance is composed of complicated mucoproteins. The colloidal state of this matrix is known to be affected by enzymes such as hyaluronidase. Various female sex hormones are known to exert opposite influence (Sprunt²⁸). By repeated injections of estrogen L. Loeb and his associates²⁹ produced hyaline changes in the stroma of various organs and H. Selye³⁰ provoked strikingly mucinous edema of the skin in hairless mice by the application of estradiol to the skin. The relation of ascorbic acid to the formation of fibers from the ground substance has been ascertained by Wolbach and Howe.³¹ Bacterial enzymes have been discovered which act as collagenases. It is necessary to unite these fragmentary observations in a comprehensive rational system. By means of purposeful experimental studies in morphology we must try to identify the structural alteration of connective tissue in terms of reactions to well-defined chemical and physical influences. The term diseases of the collagen system merely refers to the fact that alterations of the extracellular portions of the connective tissue are prominent and systemic in various diseases. Such a designation would seem to lump together such heterogeneous maladies as disseminated lupus erythematosus, generalized scleroderma, rheumatic fever, and even periarteritis nodosa. This result would be regrettable. By calling attention to the collagen tissue as a common denominator, we only wanted to indicate that this tissue may be the common anatomic site of several diseases. But we have also stressed the dissimilarities, such as the characteristic granulomatous proliferation in rheumatic fever and periarteritis nodosa and the prominent sclerosing collagen alteration in scleroderma. In referring to fibrinoid changes of collagen as a phenomenon common to all these morbid entities we must not fail to emphasize that fibrinoid change can be provoked by a variety of factors. Consequently its occurrence in different diseases must not be interpreted as indicating that these diseases are identical or even related. Parenthetically it still seems necessary to inquire whether the apparent microscopic identity of fibrinoid collagen in such heterogeneous situations might not be a delusion. Investigations of the ultimate

structure of the collagenous tissue under controlled conditions must precede further inquiry into diseases characterized by lesions of this tissue. Only if we penetrate to the basic factors responsible for aberration of structure of the collagenous tissue shall we be able to define the diverse entities which constitute the group collectively termed diseases of the collagenous system.

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STREPTOMYCIN DOSAGE SCHEDULES FOR CLINICAL USE* * *

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FOLLOWING the original publication on streptomycin by Schatz, Bugie and Waksman,¹ various exploratory clinical and laboratory investigations^{2, 3, 4, 5, 6} were reported which demonstrated the effectiveness of streptomycin in treatment of certain microbic diseases. Additional significant contributions^{7, 8, 9, 10, 11, 12} have appeared dealing with the pharmacology and toxicology of this antibiotic. In view of these encouraging reports, additional study of the factors involved in planning a treatment program for clinical use of streptomycin seemed appropriate, the primary purpose being the formulation of simplified, rational dosage schedules. The presentation and analysis of pertinent data is the subject matter of this communication.

Oral administration of streptomycin is not feasible inasmuch as the drug is not absorbed consistently or in satisfactory concentration from the gastrointestinal tract. Inasmuch as intravenous administration of the presently available supply of streptomycin frequently induces pyrogenic reactions and other toxic manifestations the intramuscular route, apart from technical considerations, is the method of choice.

METHODS

Blood levels were determined periodically for 24 to 36 hours following a single intramuscular injection of streptomycin† in varying dosages. Concomitant assays were made of the urinary excretion of the antibiotic. The method for estimating streptomycin concentrations in body fluids¹³ which was employed in this study, is a modification and adaptation of the technic developed for assaying penicillin.¹⁴ The assay for streptomycin was made more sensitive and selective by adapting *Klebsi-*

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ella pneumoniae #41 as test organism. This organism is readily inhibited by streptomycin and is resistant to penicillin. The test under these circumstances has the added advantage of being applicable in those instances where streptomycin and penicillin are combined in the treatment program.

The procedure for performing the in vitro sensitivity test for streptomycin is as follows:

Test tube sensitivity to streptomycin is determined in essentially the same manner as penicillin sensitivity.¹⁵ Bacteriostatic and minimal lethal dosage end points are estimated. The test medium is brain heart infusion broth (Difco) and the standard contains 800 micrograms per c.c. in water. Thirteen test tubes are prepared; 1.6 c.c. of broth is apportioned to the first tube, and 1 c.c. to the succeeding 12 tubes. Four-tenths c.c. of the streptomycin standard is added to the first tube and two-fold dilutions are made in the following 11 of the set up tubes. The last tube serves as control. This gives a reading range between 80-0.04 micrograms (Fig. 1). The organisms to be tested are grown in brain heart infusion broth for 18 hours and, depending upon the density of the culture, diluted 10^{-3} , or 10^{-4} . One c.c. of the diluted culture is inoculated into each of the 13 tubes. The tubes are then incubated overnight and read for bacteriostasis. All tubes with evidence of growth are discarded; the remaining tubes receive an additional 10 c.c. of broth and are reincubated for 24 hours. The test is then read for the minimal lethal dosage end point.

RESULTS

A composite graph (Fig. 2) reveals the consistent presence of detectable amounts of streptomycin in the blood stream for 24-36 hours following a single intramuscular injection of 0.25, 0.5 and 1 gm. of the antibiotic in aqueous solution. Maximum levels were achieved within the first 12 hours followed by gradual tapering off to still assayable levels within the ensuing 12 hour period.

FIGURE 1—DILUTION SCALE

Tube No.	1	2	3	4	5	6	7	8	9	10	11	12	Control
Micrograms	80	40	20	10	5	2.5	1.25	0.63	0.32	0.16	0.08	0.04	0

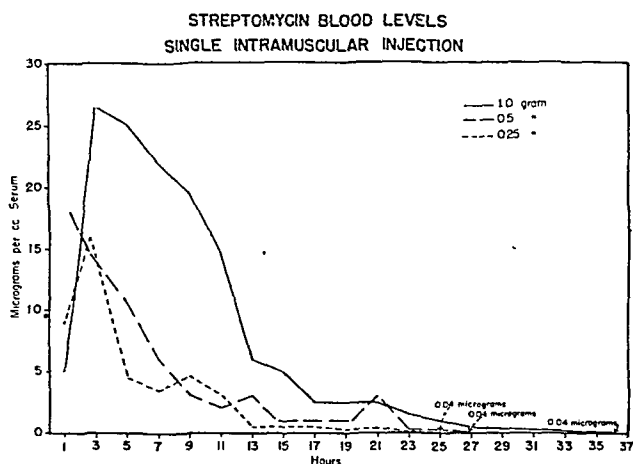


Fig. 2

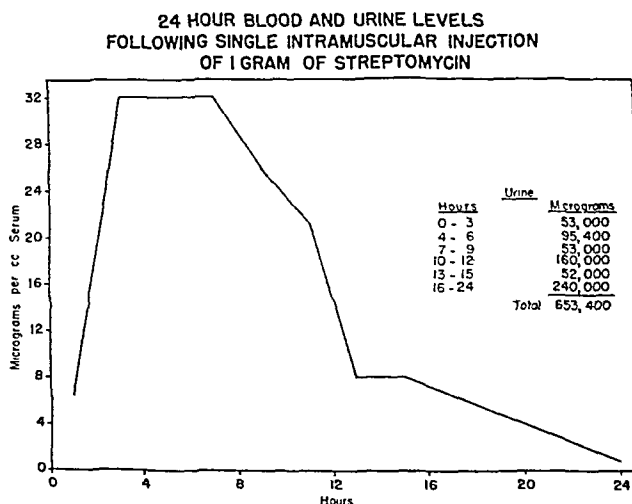


Fig. 3

At peak levels, the average streptomycin values ranged from 16 to 26 micrograms per c.c. of blood. The levels following the injection of 0.5 gm. reached a peak of 18 micrograms within one hour and then leveled off to 8.5, 6 and 4.5 micrograms at the sixth, seventh, and eighth hours, respectively. These concentrations are considered adequate for many of the streptomycin inhibitable organisms.

The curve of urinary excretion of streptomycin may parallel that of the blood concentration. A graph of values (Fig. 3) following a single intramuscular injection of 1 gm. of streptomycin portrays such parallelism and also indicates the retarded tempo with which the anti-

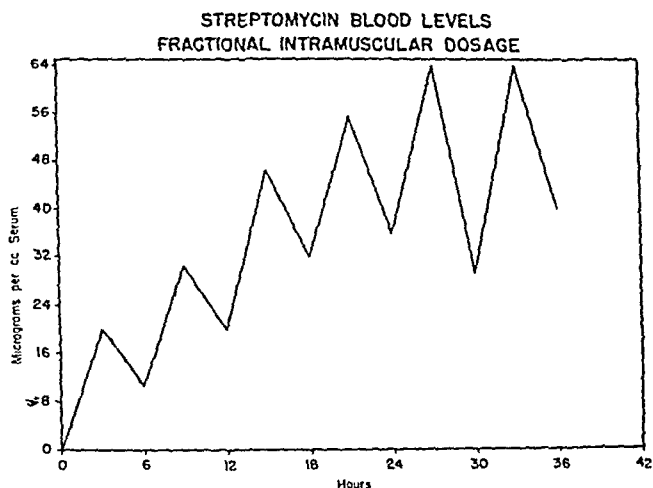


Fig. 4

biotic was eliminated. It is observed that, unlike penicillin where 60 per cent of a given dose may be recovered in the urine within one hour, in the case of streptomycin this was distributed over a period of 24 hours. A plateau type of excretion was apparent rather than an abrupt rise and fall.

In another series of studies blood levels were assayed periodically following repeated 6 hourly injections of 0.5 gm. of streptomycin. The graph of the levels (Fig. 4) clearly indicates additive, cumulative effects until a period of equilibration was achieved. The peak level of 64 micrograms per c.c. of blood is adequate for many of the microbic diseases amenable to streptomycin therapy. Ideally, the blood levels of antibiotics, particularly in the case of streptomycin, should far exceed the in vitro sensitivity value for the infecting organisms.

DISCUSSION

The intermittent, intramuscular injection of aqueous solutions of antibiotics is irksome when repeated every 3 or 4 hours. This schedule is mandatory for penicillin because of the precipitate manner with which it is eliminated by the kidneys. Studies of penicillin excretion indicate that some 80 per cent of the antibiotic is lost through the renal tubular excretory apparatus, 60 per cent of a given single intramuscular dose being expended within the first hour of its administration.^{16, 17, 18, 19, 20}

As a result of this phenomenon, methods have been developed for

retarding the absorption of penicillin and prolonging blood levels by means of intramuscular or subcutaneous repositories.^{21, 22, 23} Other expedients, like sodium para-amino-hippurate, have been adopted for blocking the transport mechanism of the kidney thereby enhancing penicillin blood levels.^{24, 25}

Pharmacological studies^{7, 8, 9, 10} have shown that streptomycin looks primarily to glomerular filtration for its excretion. This makes for a much slower tempo of elimination through the kidneys with resulting augmentation and prolongation of streptomycin levels in the body fluids. The results of our own studies (Fig. 2, 3, 4) have confirmed the fact that streptomycin is excreted at a retarded rate as compared with penicillin. Peak levels were obtained for 6-8 hours and appreciable amounts were found in the urine for 24 hour periods following a single intramuscular injection of 0.25, 0.5 and 1.0 gm. of streptomycin.

Individual dosage is predicated on the *in vitro* streptomycin sensitivity tests of the infecting organism. It is important in antibiotic therapy, as previously reported,¹⁵ to estimate both bacteriostatic and minimal lethal dosages according to the technique herein described. Studies in our laboratory have shown that dosage schedules dependent upon only the bacteriostatic activity of an antibiotic may be misleading especially when dealing with a protracted and refractory disease such as subacute bacterial endocarditis.^{25, 26, 27, 28} In the course of our studies with antibiotic therapy, we realized the importance of determining the *in vitro* minimal lethal dose for the infecting organism in addition to the bacteriostatic end point and we accordingly modified our assays. Many treatment failures were thus avoided.

In correlating our investigative data in terms of the foregoing, it may be stated that for routine use with most of the streptomycin inhibitable organisms the dosage schedule of 0.5 gm. of streptomycin given intramuscularly every 6 hours will suffice. In point of fact, studies have indicated that adequate blood levels may be obtained for most of the treatment day when 0.5 gm. is given but twice daily. This dosage plan, however, is not recommended because of the well-known property of streptomycin to induce organism resistance or even fastness with subcurative doses. The dosage schedule should, of course, be intensified up to the limit of tolerance, a total of 10 gm. daily, if indicated by the *in vitro* sensitivity value of the infecting organism.

The tendency for some bacterial strains to develop resistance to

streptomycin despite presumably adequate dosages, militates against this antibiotic agent. Additional disadvantages are the untoward reactions observed with streptomycin therapy.^{3, 6, 7, 11, 12} The most frequent and serious of these toxic manifestations are the labyrinthine disturbances characterized by nystagmus, vertigo and unsteadiness in gait which may develop within 2 or 3 days after inaugurating therapy. The longer the span of treatment, the more likely will these complications supervene.

In order to obviate organism refractoriness, forestall serious involvement of the central nervous system and prevent pyrogenic reactions the intramuscular administration of 0.5 gm. of streptomycin every 6 hours for a span of 7-14 days is recommended as a conventional treatment program. In those instances where a longer span of treatment (4-5 weeks) is required because of the nature of the infection, toxic complications may almost uniformly be anticipated. In these cases it is suggested that the treatment be interrupted every two weeks for a variable period of days depending on the response of the patient and the clinical manifestations. In any event, a total dosage of 2 gm. per day, fractionated every 6 hours, is a simple, effective and convenient method of administering streptomycin.

CONCLUSION

The intramuscular administration of streptomycin is the method of choice. Streptomycin is retained in the blood in effective therapeutic concentration for relatively long periods of time thereby permitting a more convenient spacing of the intramuscular injections. Studies are in progress with retarding menstrums to level off the peaks and achieve still more prolonged effects.*

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BULLETIN OF THE NEW YORK
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



NOVEMBER 1947

OPENING ADDRESS*

Twentieth Graduate Fortnight

GEORGE BAEHR

President, The New York Academy of Medicine

I T is now twenty years since The New York Academy of Medicine organized its first Graduate Fortnight in response to the need of physicians of the metropolitan area and of adjacent states for an annual review of the major advances in one important branch of medicine. Each year a new subject has been chosen, each year the lectures, demonstrations, hospital clinics, round table conferences, and exhibits have been better than ever before, and each year the growing attendance by several thousands of visiting physicians testifies to their appreciation of the educational value of the Fortnight. Experts from many parts of the country have generously contributed their knowledge and experience to that of our own professional and scientific leaders until the Fortnight has become one of the great intellectual treats of our country.

Throughout the year, the monthly stated meetings of the whole Academy and the monthly meetings of the twelve clinical and scientific Sections of the Academy bring to the medical profession of this area the newest information upon the important subjects of the day and

* October 6, 1947.

introduce to them many of the most important recent contributors to the advancement of the medical sciences. Other special lectures and demonstrations are given whenever opportune at other times during the year. Many clinical and scientific societies affiliated with the Academy hold their meetings within the building so that on some evenings as many as four or five meetings on different subjects may be going on simultaneously. To add still further to the educational opportunities of the medical profession, the Academy conducts, as you know, one of the largest and most used medical libraries in the world, which is freely open to all physicians and to the public until 5 in the afternoon. The Academy also maintains a well staffed educational bureau for physicians from this country, from Latin America and from abroad who seek information concerning educational opportunities in municipal and voluntary hospitals and teaching centers of this great city. For the benefit of visiting surgeons, a bulletin is published daily of the operations and the operating surgeons in every important hospital in the city so that anyone can observe any operation he may desire to witness on almost any day in the week.

These and other educational activities of the Academy are designed to make New York City the medical capital as it is already the political capital of the world. The physicians of this part of the country are the chief beneficiaries from these services, for they have the constant opportunity to enjoy them. I often wonder how many of you give a thought to the question where the money comes from for the support of all this. The library alone requires an expenditure of almost \$135,000 a year. You will be surprised to know that the dues from Fellows and Associate Fellows are only sufficient to defray one-fifth of the annual operating budget of the Academy. Part of the remainder is met out of income from endowments and bequests. But a substantial part of the annual budget depends upon gifts from the public and from physicians who appreciate the work which the Academy is doing in the fields of medical education, public health, public education and through our great library.

There is, perhaps, not a physician in this city who has not benefitted from the Academy's facilities and activities, and through the medical profession the entire public has been well served for more than one hundred years. Like all institutions of learning, our operating costs have increased greatly in recent years due to essential increases in salaries,

yet income has remained stationary. More than ever before, we must look to the public and to the medical profession for assistance in carrying their share of the burden.

This Graduate Fortnight will demonstrate that the Academy has not stinted because of increasing costs nor reduced the quality and scope of its service to the profession and to the public. Experts have again been brought from other centers of education and research. The exhibits on the subjects of the Fortnight, the Diseases of Metabolism and of the Endocrine Glands, are more extensive and more carefully planned than ever before. We are deeply indebted to the Subcommittee on the Graduate Fortnight and, especially, to its chairman, Dr. Milton J. Raisbeck, to the director of scientific exhibits, Dr. Alfred Angrist, to Dr. B. S. Oppenheimer, chairman of the Committee on Hospital Clinics, and to Dr. Charles F. Tenney, chairman of the Committee on Panel Discussions, for their devoted and valuable work. We are also in debt to the cooperating hospitals which have again organized a series of public clinics for every afternoon throughout the Fortnight. Our one regret is that the absence of permanent exhibition space makes it impossible to continue the exhibits beyond the period of two weeks and that this invaluable teaching material must then be dismantled and disbursed.

With this expression of our deep appreciation for the labor of the many contributors to the forthcoming lectures, clinics, demonstrations, panel discussions, and scientific exhibits, I now officially open this Twentieth Graduate Fortnight of the Academy.

PSYCHOSOMATIC ASPECTS OF ALLERGIC DISORDERS*

EDWARD WEISS

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PSYCHOSOMATIC is a new term, but it describes an approach to medicine as old as the art of healing itself. It is not a new specialty but is rather a point of view which applies to all aspects of medicine and surgery. It does not mean less study of the soma; it only means more study of the psyche. Its subject matter is founded on the important advances in physical medicine as well as on the biologically oriented psychology of Freud, without whose epochal discoveries no work on psychosomatic medicine could be attempted. It is not a new discovery, but rather a reaffirmation of the ancient principle that the mind and the body are interactive and interdependent, a principle that has always guided the intelligent general practitioner. As a science, psychosomatic medicine aims at discovering the precise nature of this relationship.

Allergy and psychosomatic medicine have much in common. The allergic population and the neurotic population are so numerous that they must overlap. Therefore, if for no other reason, these disorders exist together in many people.

There are other reasons why allergists and those interested in psychosomatic medicine should be interested in one another's problems. The subjects of allergy and psychosomatic medicine coincide in many ways. Applied in an empirical way for many years, both subjects were established on a firm scientific footing after World War I and both saw a more complete integration into general medicine in World War II. Utilized to some extent by many practitioners, both subjects must become a part of the understanding of all physicians. In order to accomplish this, increased facilities must be established in medical education for undergraduates and graduates. But they have more in common than this. Both have been exploited by irregular practitioners when orthodox medicine has disdained to endorse them, and both have

* Presented February 6, 1947 at the Stated Meeting of The New York Academy of Medicine.

potentialities for doing harm as well as good.

In addition to these aspects which they have in common, there is an intimate relation between them. Psychosomatic medicine would seem to have a special application to allergy. It has long been recognized that emotional factors entered into the problems of allergy, but up until recently we have lacked any exact methods of measuring these effects.

Within the last decade, however, medicine has succeeded to a considerable extent in substituting scientific principles of psychopathology and psychotherapy for intuition—generally spoken of as the art of medicine—in regard to many medical problems, and this rapidly increasing body of knowledge is now referred to as psychosomatic medicine. The subject received great impetus from military medicine because of the large number of neuropsychiatric and psychosomatic problems necessitating rejection or discharge from the service. Therefore, it would seem timely to apply some of these principles to the study of problems in allergy.

THE PSYCHOSOMATIC POINT OF VIEW

When a person gets sick he is sick all over, that is, the body and mind are one, and he gets sick for a variety of reasons, physical and psychic. In other words, it is usually not one thing that determines illness; there are multiple factors acting together. Halliday¹ points out that in our approach to illness we must think: (1) What kind of a *person* are we dealing with (inherited and acquired characteristics, physical and psychologic); (2) What has he *met* (germs, allergens, or emotionally disturbing events); (3) What has *happened* (the physiologic mechanism or pathogenesis of the disorder). For example, allergic responses occur when a prepared organism, possessing certain physical and psychologic characteristics, meets certain elements, physiologic and psychologic. In some allergic disorders a single preponderant factor may be largely responsible, as for example in pollen hay fever. In others, such as asthma, there are frequently multiple interrelated factors, allergens and psychic disturbances, which act in a complementary fashion to produce the disorder.

The psychosomatic point of view is that the psyche enters, or better emerges, as one of the several factors which, acting together, disturb the function of the organism. We will leave aside the great problem of

how much of the illness depends upon constitutional factors and to what extent special life experiences are responsible. It is the old question of heredity and environment, nature and nurture, and we have no way of delimiting them with exact measurements.

In general, physicians look upon the problem of psychic factors in illness in several ways. There is a group which considers the physical factors as being all important and indeed wholly responsible for any personality changes—"Why shouldn't he be nervous after having had such a serious disease so long." This thinking applies especially to chronic disorders such as asthma. At the opposite pole are the protagonists for psychogenesis—the psyche is all important in the determination of chronic illness. In between are those who believe that physical and psychologic aspects are but different phases of the disordered constitution, perhaps parallel manifestations of the same basic fault, existing together and related to one another. As Kubie² states, psychologic forces and somatic manifestations may have their roots in the same unconscious processes which discharge partly on the level of psychic representation through thoughts and feelings and partly on the physiologic level through the autonomic nervous system. This is the viewpoint presented here. We are not interested in proving psychogenesis, we are only interested in studying the psychic factor in illness, just as we study physical factors, and relate them if possible. We would like the psyche to be treated with as much respect as germs or allergens.

Just as we insist on this unity regarding the nature of illness—the body and mind are one—so do we urge that the means of investigation are two—physical and psychologic—and that their simultaneous application represents psychosomatic diagnosis.³ And they are applied simultaneously although their application is often unconscious and unscientific. The physician in his usual approach to the patient, using the orthodox methods of medical history, physical examination, and laboratory studies, at the same time makes many intuitive observations about the unconscious mental processes of the patient as exhibited in his language and behavior. What we suggest is that order be brought into this intuitive process. We now have enough understanding so that we can begin to forge a scientific instrument in the exploration of unconscious processes. In other words we are trying to make the rules regarding psychologic exploration as exact as the rules of physical investigation.

Psychosomatic diagnosis depends much more upon the history than it does upon physical examination or laboratory studies. This is especially true in regard to psychosomatic affections.* The faulty concept of functional versus organic disease and the necessity for giving up the "either-or" diagnostic approach have been discussed elsewhere.⁴ Personality study will show that psychosomatic disorders have their own distinctive features and that diagnosis must be established on positive data from psychologic study as well as negative data from an organic standpoint.

Rather than be satisfied with loose terminology—neurogenic factors, emotional upsets, physical and mental fatigue, emotional stress and strain—we must make an effort to define the specific emotional problem and relate it to the total personality makeup of the individual.

Just as we try to establish certain postulates for an allergic problem, hay fever for example, (1) heredity, (2) seasonal history, (3) skin tests, (4) anti-bodies, (5) induction of an attack with pollen, (6) hypsensitization or avoidance of offending substance in controlling attacks; so in the psychosomatic problem we try to establish (1) the family history (heredity and pseudo-heredity), (2) evidence for a childhood neurosis, (3) sensitivity to specific emotional factors (temporal relationship of present illness and emotionally disturbing event), especially at epochal or crucial life periods (puberty, marriage, childbirth, climacteric, etc.), (4) a specific personality structure (other evidence of neurosis or character disturbance), (5) demonstration of specific behavior on taking the history (artificial exposure to a conflict situation), (6) hypsensitization by psychotherapy or the avoidance of the provocative situation. We will not be able to establish all of these postulates in every case. For example, evidence for a childhood neurosis will often be missing—neither the patient nor his family can recall disturbed behavior or bodily dysfunction.

So far as allergy is concerned the fact that the removal of an allergen or a hypsensitization process "cures" the patient proves only that one factor has been removed and the morbid chain of events interrupted. Exactly the same reasoning can be applied to psychologic factors.

* The term psychosomatic as used in this paper indicates: (1) a method of approach to general medical problems, the simultaneous application of physiologic and psychologic techniques to the study of illness in preparation for comprehensive medical care; (2) in a more limited sense, a disorder which can be understood only when psychologic as well as physiologic factors are taken into consideration (Halliday).

ORGAN NEUROSES

Certain psychosomatic disorders have been spoken of as organ neuroses. From a psychologic standpoint there are different varieties of organ neuroses depending upon the severity of the underlying disorder. There are very mild disturbances of organ functioning, psychosomatic dysfunction, which are hysterical symptoms. They are spoken of as conversion phenomena, a substitute expression of an emotional tension which cannot find adequate outlet. The substitute expression is symbolic, i.e., nervous vomiting may, as part of its meaning, express unconscious disgust. There are other disorders, however, which have been referred to as vegetative neuroses. These arise not as an attempt to express an emotion but as the physiologic accompaniment of constant or recurring emotional states. Here the somatic symptoms are not as much substitute expressions of repressed emotions as they are normal physiologic accompaniments of the emotional state (Alexander⁵). They are the adjustment of the organism to definite tasks which it has to face in a danger situation. They represent a utilitarian preparation and an adaptation of the internal vegetative processes (homeostasis) to a specific type of behavior which is requested from the organism. It may then be that the chronicity of the emotional tension (plus other factors) makes the condition morbid-psychosomatic organic disease. Any vegetative nervous system disturbances, such as the allergic disorders, deserve study of the psychic as well as the soma and often will prove to be psychosomatic affections.

The emotions often exploit an organic illness and thus it is that frequently following an infectious disease or operation convalescence lingers and invalidism sets in. The explanation so often given is that the organic disease produced the neurosis whereas the actual mechanism is that the organic process has broken down the individual's defenses, regression occurs, and the individual's predisposition, determined by the personality structure, permits the neurosis to emerge.

An important subject in psychosomatic illness is the shift from somatic expression to the mental sphere. Very often in the organ neuroses the improvement of a symptom because of treatment or for any other reason may lead to mental symptoms such as mood disturbances and sometimes to manic and depressive states. An important therapeutic lesson comes out of this consideration because sometimes in psychoso-

matic illness when we get rid of symptoms by means of medicine, surgery, or manipulation, without getting at the fundamental problem—the emotional conflict—the difficulty immediately is reflected in mental symptoms.

DEFINITIVE DIAGNOSIS

Just as in a consideration of somatic disease it is necessary to make a complete diagnosis before we can hope to apply scientific treatment so it is equally necessary in psychosomatic medicine. Hence just as in general medical teaching we have always emphasized etiologic, anatomic, and functional diagnosis, so in psychologic medicine, as pointed out by Levine,⁶ it is necessary to make a clinical, dynamic, and genetic diagnosis before one can stand on safe ground in regard to psychotherapy.

The clinical diagnosis in psychosomatic medicine refers to the structural and physiologic deviations as well as to the underlying or associated psychologic disturbance. For example, in the so-called organ neurosis, we would like to know whether we are dealing with a mild personality disorder such as hysteria or a severe personality disorder such as hypochondriasis. It is important, for example, in asthma, to know whether the symptoms are on the basis of conversion hysteria or a part of the clinical picture of depression in which the mood disturbance is overshadowed by the somatic complaints. When one deals with depression there is often the threat of suicide.

Dynamic diagnosis refers to the meaning and purpose of the symptoms or behavior in terms of the particular personality and its structure. Coupled with the genetic diagnosis which is derived from the longitudinal survey of the individual life history, we are then in a position to plan comprehensive medical care.

ASTHMA

I am not going to attempt a complete discussion of the allergic disorders. I shall select asthma first, because it is the one field in which allergists have been very willing to concede the presence of a psychological factor, and I think it is probably the one disorder that those interested in psychosomatic medicine have had the greatest opportunity to study.

Just as the heart is sometimes referred to as the seat of emotions

and the abdomen as the sounding board of the emotions, so the lungs might be spoken of as the barometer of the emotions. Under certain circumstances we catch our breath, or we complain of smothered feelings. We have shortness of breath, which represents not dyspnea, but sighing respirations which are so common in neurotic people. We speak of a person having a load on his chest, the implication being that he could get it off by talking about his troubles. Some of these symptoms will be recognized, of course, as hysterical mechanisms, the symbolic expression of tension, or to put it another way, when people are unable to act or unable to speak about a problem, the body takes over the function of answering that problem in its own way.

To go back to a former example, if someone is vomiting and no organic cause can be found, we ask the question—What is it in his environment that the individual cannot stomach? And sometimes we get at least part of the answer. In the same way we can sometimes find the cause of a load on the chest. While it may represent a respiratory disorder, it is not in the lungs; it is in the spirit of the individual, in his feelings. In other words, feelings may be as potent as germs or allergens in causing disturbances of function.

One of the things that we will have to learn in medicine is that the things people say are sometimes just as important as the sounds that their organs make. This applies especially to bronchial asthma. In other words, if we pay more attention to what people say, we will often realize that the words they produce, representing their thought processes, are the secretions of the mental apparatus, just as the urine is the secretion of the urinary apparatus, and that both can be analyzed for diagnostic and prognostic purposes.

In this connection, I would like to quote from a paper by Binger⁷ on the psychobiology of breathing, in which he pointed out that the respiratory apparatus is genetically and structurally related to the gastrointestinal tract and that in many ways they seem to function similarly. Embryologically the pulmonary respiratory apparatus develops from the hind part of the ventral wall of the head gut, and he points out that both systems are concerned with the incorporation of certain substances from the external environment, with the transport of these substances to tissue cells, and with the excretion of certain products of tissue metabolism. He indicates that the digestive and respiratory systems can be susceptible to similar derangements, such as spasms and

secretory changes, and that both may be the pathways for entrance of infectious organisms. He goes on to say that if Alexander is correct in his assumption that the gastrointestinal tract may act out certain emotional trends having to do with ingestion, retention, and elimination, it is conceivable that an organ system so closely parallel embryologically and functionally can exhibit similar responses. Indeed, Alexander and Saul⁸ have analyzed respiratory tracings with special reference to psychological behavior and felt that there was suggestive evidence of a relation between intaking and eliminating tendencies, observable in the emotional life and in certain characteristics of the spiograms.

In the past twenty years or more, many observations have been made and articles written on the relation of the emotions to bronchial asthma. Neurotic trends have been recognized, but, as in other organ neuroses, very often have been held to be due to the disease rather than causally related to it. It has been noted that the sufferer from asthma often seems to make the most of his attack by drawing attention to himself and by his distress disturbing those around him to the utmost. I think many of us now recognize that this is not fundamentally responsible, but it is just a secondary gain, the utilization that the patient makes of his illness, because the psychological factors that we think are related are far deeper in the unconscious mental life and have no such thinly disguised purpose. They reveal themselves only after more patient study.

McDermott and Cobb⁹ in a clinical survey of fifty cases of bronchial asthma found that thirty patients showed neurotic traits other than the asthmatic and that these were usually of a compulsive character. Rogerson and associates¹⁰ have studied children with what they call the asthma-eczema-prurigo syndrome, and they report that out of twenty-three, no less than seventeen were very overprotected by their parents, and they raised the question as to whether the difficulties produced by the disease itself had to do with this over-protection; but they go on to say that in their cases, carefully observed, it was plain that the over-protective attitude of the parents existed prior to the onset of the asthma and had a deeper motivation, such as a need to over-compensate for not wanting the child, the fears of losing the only surviving child, and a number of other reasons.

Then there is some evidence from Rorschach studies on asthmatic patients suggesting that the personality disturbance existed before the

onset of the disorder. The Rorschach test, a projection test of the personality, has been widely used in recent years and seems to be one of the outstanding methods of personality evaluation. Schatia,¹¹ who analyzed the Rorschach records of forty patients suffering from bronchial asthma, confirmed an impression gained by a number of analytical workers that asthmatics tend to have compulsive personalities without evidence of phobia or compulsion. Dunbar¹² called attention to this fact in 1938, and Felix Deutsch¹³ made similar observations from psychoanalytic study.

The most detailed psychological study of bronchial asthma is probably now familiar to you, the publication by French and Alexander¹⁴ and their associates at the Institute of Psychoanalysis of Chicago who studied twenty-seven cases by means of psychoanalysis.

They observed, first of all, that the patients varied a good deal in their personality traits, but one thing that existed in common was a very dependent and infantile relationship to the mother and that an attack of asthma would often occur when the patient was exposed to a situation that threatened to estrange him from the mother. This might occur in an actual life situation, in a dream, or in relationship to the physician. The attack of asthma often occurred at the point where the defenses of the individual failed and where he was suddenly exposed to the conflict between an actual life situation and the fear of losing the mother's love. These emotions often were transferred to the physician in the course of treatment so that the patient's fear of losing the goodwill of the physician would sometimes take the place of the original fear of losing the mother's love. Over and over again, French found that these patients would become blocked just at the point where their unconscious material was leading them up to make some kind of a confession, which represented an attempt at reconciliation with the parental figure. They would be afraid to confess and instead would develop an attack of asthma. As long as the technique of winning reconciliation with the mother by means of confession was successful, the patients appeared to be protected from asthmatic attacks. When the confession got choked in the throat, so to speak, an asthmatic attack occurred in its place.

French believes that throughout the lives of patients subject to psychogenic asthma attacks, there seems to run a continuous undercurrent, more or less deeply repressed, of fear of estrangement from the mother

upon whom the patient is usually very dependent in an infantile way. The cause of this fear of estrangement is usually the patient's own forbidden impulses which he thinks will offend the mother. A device that the asthmatic patient makes extensive use of to protect himself against this danger of estrangement is confession of the disturbing impulse. If the mother or mother substitute, in this case the analyst, accepts the confession without being shocked, then all is well for a time. If the patient is too uncertain of the mother's tolerance to dare make the confession, then an asthmatic attack is likely to be precipitated.

Psychic and Allergic Factors Complementary—Finally French and his colleagues conclude that psychological and allergic factors stand in a complementary relationship to each other in the etiology of bronchial asthma; that in some cases asthma attacks may be precipitated by allergic factors alone, in others by emotional factors alone, and in still others the combination of allergic and emotional factors seems necessary to bring about an attack.

Let me cite a case to illustrate some of this material.

Mrs. K. M., a healthy appearing, young woman, was first seen in June, 1946. She reported that she had had severe asthma since early childhood and had known only a few periods of real freedom in the more than twenty years that she suffered from this disorder—during the time that she was away at school and during her two pregnancies. She also had eczema as a child, and on a few occasions since, and vasomotor rhinitis which had been quite bothersome in recent years.

The mother suffered from migraine and had asthma in her early years and a brother had hay fever. The father had died of heart disease in 1942.

The patient reported that eczema began in early infancy and that asthma occurred at about the age of two and this was confirmed by the mother. The asthma became quite severe about the age of seven and she was studied in a large hospital where allergic tests were made for the first time. These had been repeated frequently since, the last time three years ago in the course of a complete study at a well known clinic. Certain foods were denied the patient which she says she eats with impunity during the periods when she has been free of asthma.

Physical examination showed a robust young woman with no evidence of eczema, rhinitis, or asthma at the time of examination. She appeared to be in good health and no evidence of organic disease was

detected. Routine laboratory studies were negative.

She was an obedient child who was taught cleanliness early. She was brought up in a small community where the parents were in comfortable circumstances so that she enjoyed all of the material possessions that a child could want. In fact she reported that her father, a tense, nervous, and domineering person "gave gifts instead of understanding." He demanded exacting obedience and the patient resented his treatment of her as well as of the mother. The father was particularly emphatic in his instructions to the young girl regarding men so that she was constantly warned about the dangers of murder and rape. Pity for the mother, the mother's air of martyrdom, and her threats of withholding love, forced the child into a submissive attitude. She tried to make up to the mother for the way the husband treated her.

She looked to the mother for approval, was very dependent upon her and yet, as she reached later childhood, found difficulty in accepting gifts from the mother. She felt that there was something wrong about doing so and this feeling has continued to the present time. Apparently accepting a gift was an indication of the dependence against which she struggles. When she went away to school, for the first time she became free of asthma for a long period and the asthma would recur only when she returned home at vacation time. In the junior year she was assailed with doubt regarding her choice of career but was afraid to change because of the mother. In order to solve the problem she became engaged, married the following year, and immediately became pregnant "in order not to have to finish school." She was well during the pregnancy but a few weeks after the birth of the child asthma began again and she then decided to leave home and move to Philadelphia. The father objected but she left anyhow and shortly afterwards the father died of heart disease. She felt no grief, "only a slight guilty feeling"—if she had not left "this might not have happened."

Sexual intercourse, which had been painful before the birth of the child, continued unsatisfactory. She became concerned about frigidity and decided to consult a physician but again asthma interfered. Another period of hospital observation failed to help the patient and she and her husband decided to move to Florida. However she did not do well there and they ran into great difficulties with the husband trying to earn a living and take care of the sick mother and child. The patient came North to visit the mother who had remarried so that she no

longer had to worry about the mother "being alone," but the asthma continued. When her child was three she decided that having been well during pregnancy another pregnancy would be helpful. True enough she again felt completely well during the second pregnancy but again developed severe asthma shortly afterwards. Now the husband's difficulties were redoubled because he not only had to work harder to earn a living but had a very sick wife and two young children to look after. The patient went from doctor to doctor and finally one suggested that emotional factors must have something to do with her illness. For the first time she began to think of her illness from that standpoint and, recalling that during her school days she was entirely comfortable away from home and sick as soon as she got home, she concluded that her relationship to her mother must be the reason.

Now as the patient "thought the problem out for herself" she went through a very bad period. She was sleepless and despondent, had a "terrible, queer, detached feeling," as if she were in another world, suffered from dizziness, pressure on the head, blurred vision, had fears that she would lose her mind or commit suicide, and was unable to be alone with the children for fear that she might harm them. Her physician was in constant attendance and she poured out to him many of the thoughts regarding her life and her relationship to her parents, husband, and children. She spoke of resentment against the father, of her hated dependence upon her mother, and of a nameless resentment against the husband "as though she would like to throw a knife at him." At the same time she admitted that he was an extremely able person and an excellent husband. If anything "he was too good" to her. She decided that she had been escaping from life and that with the doctor's help she would learn to face things. Now her black moods came and went and at times she felt exhilarated. For the first time she was able to achieve orgasm in intercourse. She felt like a different person, as if "a new personality was emerging." She described this new person as more adult, possessing a great deal of self-confidence. For several weeks she continued in this mood and was quite free of asthma but then for reasons that she did not understand her chest tightened up again and she became as ill as before. They decided to leave Florida and on the way North by automobile she was very ill, causing the husband a great deal of distress and effort as he looked after her and the family.

After establishing herself in Philadelphia she very quickly improved

as she was encouraged to talk about her life situation. Almost her whole conversation centered on the topic of her relationship with her mother and just as she described her life up to this year as one of affection and devotion to the mother now her sentiments were just the reverse. She could find almost nothing good to say about the mother. In an interview with the mother I did not gain the impression that she was mean or malicious but it was apparent that because the mother had been deprived of love as well as material things in childhood she was determined to see that her own child was loved, protected, and denied nothing. Thus she over-protected the child, confided in her regarding her loveless marriage, and made the girl too dependent upon her by threatening her with loss of love; and these were the conclusions that the patient had reached in her self-analysis. She described the mother as an infantile person who had encouraged the child's dependence, over-protected her to satisfy the mother's emotional needs, dominated her by threatening loss of love and by her suffering and martyrdom, withheld help when it was necessary and gave gifts that were not wanted. The patient had some insight however, because she spoke of desiring a better relationship to the mother with neither the affection she had felt before nor the hostility which she now feels. The mother would call on the phone and say that she was going to visit the patient and as she would hang up the receiver the patient would develop an attack of asthma. The mother would send gifts that the patient found either impossible to accept or if she did accept them she promptly lost them. On one occasion she lost a valuable piece of jewelry and felt no remorse. This quixotic behavior was not confined to the mother, however, because on one occasion the husband gave her a \$20 bill which disappeared the next instant and was found in the baby's playpen. The husband recovered it and handed it back to her, telling her to be careful, and the next moment it was gone again. This time it was found in the waste paper basket.

Her dreams dealt with frustration. She was tied, bound, in a car that could not get up a hill, or in a plane that could not reach its destination. About the time that she was trying very hard to get established in a home she had a dream of "buying a house with a fence around it. In order to get the house she had to take the fence." Using this very obvious symbol I asked her what fenced her in and her reply was her illness, her mother, and housework. She was trapped in her adult

life as well as in her childhood by the dependent relationship upon her mother which she hated but from which she could not escape. However, it seems significant, that all of the time she was freely expressing her hostility for the mother she was free from asthma except for very minor attacks occurring in direct connection with the mother's visits, presents, or phone calls. The husband observed that when the mother visits them the patient "withdraws from him, not only sexually but in every way."

SUMMARY

A young woman suffered from asthma which began at the age of two. Eczema preceded the asthma and vasomotor rhinitis occurred in recent years. There was a family history of migraine, asthma, and hay fever. Allergic factors apparently were not important in relation to the patient's illness; psychological factors seemed to be. Such was her dependency upon the mother's love and her fear of estrangement from the mother that she married and became pregnant in order to solve a conflict in regard to finishing school rather than confess to the mother her inability to pursue a course which she no longer wanted. On another level and untouched by therapy was her disturbed relation to her father which revealed itself in her relations with her husband.

When for the first time at twenty-six it was suggested to her that emotional factors might have something to do with her asthma she went through a period of self-analysis which apparently precipitated a near-psychotic reaction. The self-analysis brought into consciousness a deeply submerged hostility to the mother so that the patient, who had previously felt only affection and respect, now could hardly abide the mother. A physical contact such as a kiss or an embrace revolted her. But in the period of conscious devotion (and repressed hostility) she suffered almost constantly from asthma while in the period in which she expressed her hostile feelings she has been comparatively well. Perhaps not entirely well because other factors, constitutional as well as psychological, also enter and moreover she cannot adequately express all of her hostility by talking. To make an adult of her would be a difficult job because of her deep infantile attachment to the mother and only prolonged psychoanalysis could hope to accomplish such a task. Since that is impossible we must get along with less and it is hoped that this may result in some permanent benefit even if "cure" is not brought about.

MIGRAINE

Migraine lies in a territory that has been fought over by allergists and psychiatrists, both claiming it for their own, but each recognizing that there are aspects of the disease that relate to the other's approach. There is considerable agreement regarding the physiological mechanisms involved. Engel and associates¹⁵ have made some observations in the course of aviation medicine experiments about a migraine-like syndrome complicating decompression sickness. They describe the scintillating scotomas, the focal neurological signs, and the headaches which emphasize the similarity between this syndrome and clinical migraine and suggest that the mechanisms are similar. Their studies confirm the observations of Wolff¹⁶ on the mechanism of the neurologic prodromes of migraine and suggest the identity of the two.

The characteristics of the neurologic disturbances indicate that they originate in the cerebral cortex and probably result from spasm of cerebral arteries. Moreover, the authors discovered a high incidence of migraine-like headaches in the subjects who were susceptible to this decompression syndrome, indicating that a predisposition to this particular type of vascular reaction is an important factor. They accept the interpretation that the scotomas and other neurologic symptoms result from cortical ischemia due to spasm of intracranial arteries, but that the headaches result from dilatation of pain-sensitive cranial arteries. The headache was not associated with any changes in the electroencephalogram and that is consistent with the experience of others in the study of clinical migraine.

Apparently these mechanisms can be set in motion by psychic stress related to the personality structure of the patient with migraine. In a review of twenty-four patients studied from a psychosomatic standpoint I was impressed with the features that they shared in common—a compulsive character, an inability to express hostile impulses adequately, the high incidence of various degrees of impotence among the men and frigidity in the women, and the patient's willingness to blame his headache upon the bowel, the sinuses, or "something he et". To the last I usually answer "no, it is probably something you met" but because of this association to the gastrointestinal tract and the willingness of the patient to blame the headache upon a disturbance in bowel function he usually becomes addicted to the laxative or enema habit

while, for the same reasons, his physician endorses the allergic approach. Blaming the disorder on the sinuses is also very common, so common in fact, that the patient often uses the expression "I've got my sinus again" rather than to say that he has a headache.

The role of repressed hostility has also been stressed in hypertension and perhaps the fact that migraine occurs so frequently in hypertensives indicates this common denominator in their psychopathology.

A careful study of migraine by means of the Rorschach method, using control groups (Ross and McNaughton¹⁷) fails to confirm the clinical finding of repressed rage but does corroborate the personality features, namely; persistence toward success, difficulty in sexual adjustment, perfectionism, conventionality, intolerance, and in general, obsessive-compulsive features. They found that these personality features are associated with migraine to a greater degree than would be accounted for by chance.

Fromm-Reichmann¹⁸ in a psychoanalytical study of eight patients with migraine found that the individual cannot express his anger properly, and he then takes it out on himself, so to speak, in an attack of migraine. It is almost as though he would punish himself for the destruction that he would like to visit upon another. The necessity for the degree of repression of hostile feelings and why the head is chosen as the organ to express the disturbance also interested her but I shall not take the time to discuss her views on these subjects.

The following case suggests this mechanism and corresponds to the postulates that I mentioned earlier for a psychosomatic affection.

A Jewess of twenty-eight, was raised in an orthodox home, where, however, in her own words, religion was applied with a light hand. She married a man who observed the orthodox tenets of his religion with an almost fanatical zeal. Although migraine headaches antedated the marriage they now become very severe and occurred quite regularly on Saturdays.

The patient came from a family that was highly intellectual, but quite psychopathic. She considered herself scholastically the black sheep, although she was really a very intelligent girl, self-educated, and had accomplished a great deal for herself. The mother had died of bronchial asthma about the time that the patient's headaches began. The patient attributed her headaches to sinus trouble.

The patient stated that she had had a sense of relief when the

mother died because the mother had been so ill with the asthma. Then the father remarried a rather ignorant woman (these were the patient's words) in sharp contrast to the patient's own mother, and apparently this had something to do with the patient's determination to get married herself.

The patient had a fear of developing asthma, because of the mother's illness, and she had also a great fear of cancer, a real cancerphobia. Just before I saw her, she had had an anxiety attack and since then she had been nervous, weak, and depressed.

She had been studied by allergists who, because of the occurrence of the headache on Saturday, suggested that something in the orthodox food rituals might be related to the attacks. So she was subjected to skin tests, and to a number of elimination diets which, however, failed to help her.

Much of her conversation had to do with her husband. She said that his whole life was religion; that his fanatical traits are especially marked on Saturday, the sabbath day; that he rushes her to get ready for that day and that she doesn't like to be rushed. There must not be a spot of dust for the holy sabbath. On one occasion, he spoke to her about the fact that he couldn't love a woman who didn't see eye to eye with him on his religion. She resented this, saying "His love of religion is enslaving me. If love is based on ritualistic observance, he can keep it. He says he can only love me if I give up my rebellious ways. I want to worship in my own way. He forces his religion on me and he won't compromise."

In addition to that fact, just when she was so irritated and fatigued by preparation for the sabbath, it was invariable on Friday nights that he asked for sexual intercourse. There is a special preparation for intercourse among those who observe the orthodox tenets, the woman has to immerse herself completely in a tub reserved for that purpose. She very much resented this preparation. She was frigid in intercourse, failed to obtain any satisfaction, and regularly on the night or the morning following she developed her attack of migraine. Before this was called to her attention she herself observed that when she was away for the summer, she didn't have migraine; in fact, she noted, "When I am away from home, I don't get migraine on Saturdays." When I pointed out her inability to express hostility directly and hence the mechanism of body language, she replied that "hers was very eloquent."

She spent the summer away from Philadelphia. On her return, after having been free of migraine, she became irritable and depressed, complained of a heavy head, spoke to me about the boredom of facing another winter; said that she felt alone even when her husband was at home.

Finally, with my persuasion she decided to get herself some employment. I suggested that she try to find something that would fall in with her husband's interests. She got a job teaching Hebrew in a rabbinical school, and derived a great deal of satisfaction from it. Her migraine improved during this period. The anxiety of the cancerphobia came up again. I discussed that with her. She said, "Yes, people sympathize with the headache, but not with anxiety. Even my husband walks around on tip-toe when I have my headache."

I cite this case to point out some of the mental mechanisms that seem to be important in migraine. I cannot deny that allergic factors may also be involved although they apparently were pretty well excluded in this case. However in other instances it is likely that psychological factors and allergic factors are complementary; that just as French stated in the study of asthma, in the one instance it may be allergic factors that bring about the attack, in another instance it may be the psychic factors, but that in so many instances one complements the other.

NEURODERMATITIS

We speak of the skin as we do of the eye, as an organ of expression. The skin and the eye and the hair sparkle, they glow with vitality or they are dull and lifeless. The skin, like the eye, is an important point of contact between the inner and outer worlds. Blushing, pallor, and sweating are well known skin phenomena that express behavior. But beyond this obvious relationship we would like to know whether emotional factors may be responsible for skin disorders.

I think the general opinion of dermatologists in this regard has been well expressed by Sulzberger¹⁹ who found no proof for nervousness as causal in the production of a dermatosis. He said, "In our material, we have gained the impression that these occasional instances of nervousness were, one, purely coincidental; two, concomitant, that is, psychoneurological disturbances caused by the same factor or factors which produced the dermatologic manifestation; or, three, the entirely

comprehensive result and the normal reaction to the dermatosis and its maddening itching, loss of sleep and continuous worry about disfigurement, etc."

Continuing, Sulzberger pointed out that the older designations of neurodermite and neurodermatitis, had nothing to do with the present meaning attached to the words nervous, neurogenic or neurotic.

In this connection, I would like to cite very briefly a case that is now old in the literature but which has some keen and critical comment that I think is still pertinent. Rattner²⁰ reported the case of a young man who two weeks after his marriage developed an acute dermatitis on his face, neck, and upper half of the body. He had a psychoneurosis and anxiety state. It was assumed that the dermatitis was a neurogenous dermatitis. It was subsequently shown, that the acute dermatitis was excited by perfume cosmetics which his wife used.

For sixteen years this patient had had recurrent attacks of eczema, all of which were considered to be seborrheic dermatitis. Then, superimposed on this seborrheic habitus, the acute dermatitis was found to be a sensitization dermatitis. The importance, if any, of the neurogenous component, Rattner went on to say, could be estimated only by inference, whereas positive patch tests were tangible evidence that the irritant was at fault.

I had some correspondence with Dr. Rattner about this case and he said that the diagnosis, neurogenous dermatitis, was made by a dermatologist in another city, only after a thorough search for irritants had failed. Another capable dermatologist concurred in the diagnosis. The patient then consulted a neuropsychiatrist who agreed that there was a psychoneurosis, but felt that the dermatitis was a thing apart.

I won't go on with the details of correspondence, except to say that the patient eventually got himself into the predicament of going to a psychiatrist for treatment of his skin and to a dermatologist to look after his psychological disturbance.

Dr. Pusey commented about this case: "We are witnessing an intense agitation of the subject of nervous eczema. Dr. Rattner's case illustrates the pitfalls into which we are apt to get in following this lead. Here is a case which seemed made to order for the diagnosis of eczema of nervous origin. The sexual element is exaggerated, the psychic factors are all there, including, as is usually found in such cases, a readiness of the patient to accept the emotional origin of his trouble.

The background is perfect and it takes but a few bold strokes of the sympathetic artist to give a striking picture of a neurogenous or psychogenous eczema. But what do the unsentimental facts show when they are worked out? The patient is sensitized to perfume and that is what is exciting his attacks. Many similar cases of nervous or other systemic origin which have vanished into thin air when they are traced down to their local irritations must occur to everyone with a large experience in skin disease."

"The insistence of the importance of nervous factors as a cause of eczema and many other dermatoses is a backward step into the old maze of conjecture, out of which we have been trying to find our way for more than a century. Each revival of the conjecture gives us a new set of terms, but the idea remains the same. Forty years ago they were treating neurasthenia by cutting off prepuces, correcting defects of vision and removing other actual or imaginary causes of reflex irritation to cure eczema. Then they called them eczemas of reflex nervous origin. Now we are psychoanalyzing them and calling them psychogenous and neurogenous eczemas. The words are new, but it is the same old tool. The ideas are remnants of the old hippocratic humoral pathology which has obfuscated our views for twenty-five years."

"One of the chief businesses of dermatology since it has been able in the last hundred years to study more accurately the physical and chemical facts of pathology has been to show in respect to one disease after another that these diatheses are broken reeds, extremely tempting and appealing in one way or another, according to the predilections of the individuals, but in the end broken reeds. When the diathesists are confronted with a case which they would have of a nervous origin but in which it has been demonstrated that the external cause which excites the eruption and without which the eruption would not exist, they are wont to take refuge—" and now you will recognize why I am quoting this in such detail—"in the explanation that the irritant is actually only one of the causes, that their theory still holds good because there are emotional or other factors in the case which may be contributory."

"That sort of reasoning," he states, "is begging the question. The same facts apply to every pathologic condition of specific origin that can be conceived. A longer list of predisposing causes can be offered for tuberculosis. One could even get up a list of respectable causes for scabies. But these predisposing factors in themselves are not the cause

of the disease. You may emphasize them and elaborate them. You may indulge in all kinds of intellectual and physical gymnastics, but they alone are impotent; without the definite, specific cause, disease does not occur. And it may be added in the case of irritant dermatides, without the discovery of the cause, treatment is likely to be ineffective."

I won't go on with his discussion any further, because I think I have demonstrated his point of view and the point of view of a great many dermatologists today. For the sake of discussion let us take a case of fungus infection of the feet recently reported by Harris.²¹ As you may know this is a condition that is often complicated by an allergic reaction.

A virile-appearing, handsome, twenty-four year old Marine had spent 210 days in naval hospitals during a two year period of service, most of this time because of recurrent fungus infection. Personality study revealed a severe anxiety neurosis manifested by a great many psychosomatic complaints, very low self-esteem, and an unmistakable feminine trend in job preference. When the data were discussed with him he admitted bisexuality. Apparently the stress of constant stimulation and threat of exposure kept him in a state of anxiety. He was given sufficient insight to understand the mechanism of his trouble: Homosexuality—anxiety state—excessive sweating of hands and feet—inability to cure the fungus infection in the presence of constant moisture.

This case of course cannot serve as an example for a complete presentation of the controversial problem because no one would contend that there is a specific relationship between this patient's personality and the fungus infection. And yet I think every one would agree that this is truly a psychosomatic problem from the standpoint that psychic and physical factors act in a complementary fashion to produce the disorder and that only by the utilization of psychological as well as physiological techniques can we understand the illness. But of course the real problem in regard to psychosomatic medicine is whether there is a specific relationship between the personality and the skin disorder and the dermatologist wants to know whether psychogenic influences can be responsible for an actual dermatosis. The following case is intended to illustrate, not prove, this proposition.

A woman of fifty had typical neurodermatitis behind the ears and the back of the neck, sometimes extending to the arms. In addition she suffered from asthma, migraine, and hypertension. The migraine

had begun in adolescence, the asthma and skin trouble had been present for perhaps fifteen years, and hypertension had been discovered in the last several years. In the beginning the migraine had been associated with menstruation which was irregular and painful. During high school she had suffered from "anemia" and had to give up school in her third year because of "fatigue." She had been free of headaches in the last several years—her physician has said "either they would wear me out or I would wear them out." But the migraine apparently was replaced by the other difficulties. The patient had given up many of her household and social activities because she was "too nervous." She slept poorly and blamed it on the irritation of the skin. She had been studied in many excellent clinics and the diagnosis of neurodermatitis was well established. Allergy studies and elimination diet had not proved helpful.

The patient had been brought up in a small mid-western town by wealthy parents. The father was a benevolent tyrant; the mother a neurotic and over-protective person. She was married at twenty-seven to an inadequate person who never made a satisfactory living. She had known him for four years but had to wait until her older sister married before she could marry. Then her marriage was disturbed by the mother's final illness and the mother's death took place a short time afterwards. The patient had had three pregnancies but only one child, a daughter now married and living in another city.

The patient had always been frigid and in the last several years the husband had become completely impotent and there was a great deal of resentment on the part of the patient. She thought that her husband was unfaithful and in an off guard moment blurted out that "she hated him." After about ten years of marriage the father died and a great deal of trouble arose in the settlement of the estate. There was a quarrel between two brothers who have not spoken since and the patient played a buffer role between them, her sympathy being with the younger brother who suffers from a heart ailment. She feels that he was cheated out of his fair share of the estate. Because they are a close-knit family living in a small community she is constantly reminded of and humiliated by the family quarrel.

She became aware of the fact that her feelings had much to do with her illness and that she had retired into herself nursing the family problems. Attention was directed to the life situation rather than just to the skin, the asthma, or the high blood pressure. In fact nothing was

done as far as the skin was concerned—it was largely ignored—while attention was centered on the main life problems of resentment against an inadequate husband, the highly charged tension of the family schism, the retirement from life's activities, preoccupation with symptoms, and the attendant neglect of personal appearance. As she learned to express her feelings and saw her problems in a somewhat different light, her attitude changed both toward her illness and toward the family situation. She was encouraged "to carry on in spite of symptoms" and this meant doing more work, such as needlework and cooking—which incidentally kept her hands busy so that she bothered her skin less. It also meant going out more socially "in spite of the appearance of the skin." Her improvement was reflected in all aspects of her personality. She became more reassured, lost twenty pounds of her excessive weight, "spruced herself up as she came out of her shell," and took up many of her former life activities. The clearing of the skin coincided with the other improvements and a check-up two years later found her in good shape even though she had returned to her former environment.

Now the question arises—are these various disorders related to one another and to the personality of the patient. Studies demonstrate that they have certain features in common—which correspond to the clinical picture of a vegetative neurosis and meet the previously discussed criteria for a psychosomatic affection. In other words there is a positive family history, evidence for childhood neurosis or psychosomatic disturbance, the personality structure of neurotic character, exacerbation at crucial life periods in connection with specific life situations, demonstration of specific behavior on exposure to a conflict situation such as may occur in a medical interview, and clearing of the skin by the hyposensitization of psychotherapy or the avoidance of the trouble by avoiding a provocative situation.

PERSONALITY TRENDS IN ALLERGIC INDIVIDUALS

Although the work that has been done on the question of the specific relationship of personality to disease is impressive it cannot be regarded as conclusive. Nevertheless certain trends within the personality seem to favor certain disturbances.

In regard to this question Saul²² calls attention to the fact that it is the oral form of attachment to the mother, consisting of a mixture of impulses, desires, and feelings which become interwoven with sucking

and later the eating mechanisms, that enters into psychosomatic gastrointestinal problems. Other biological mechanisms and forms of attachment to the mother seem to be important in the allergies. These are the dermal and respiratory. In other words, in many persons the form of attachment to the mother as seen in fantasies, dreams, and real life is not, as in many instances of gastrointestinal disorders, strongly "oral," but consists rather in a desire for shelter. The longings are represented not by wishes to be fed and all that this can imply emotionally, but rather in wishes to be sheltered and protected. Such individuals often gravitate to modes of life which gratify such tendencies. Perhaps it could be said that, given a choice, they would prefer snug housing to good food. Here, too, can be points of weakness and fixation, to form a physiological pathway for the attachment to the mother and become interwoven with powerful feelings and longings.

When the relationship to the mother, with all of its significance to the child and later in life, unconsciously, to the adult, is threatened; or when a person is under stress, the longings for help or consolation are expressed in various combinations or forms in different persons—wanting to be fed, wanting to be carried or lead, wanting to be snuggled and sheltered, and so on, reflecting the oral, ambulatory, dermal, respiratory and other mechanisms and forms of attachment to the mother. The impulses may be gratified by personal relationships, sexual or sublimated, which reestablish in some degree the relationship to the mother. The gratification may be sublimated (oral—eating and drinking; respiratory—talking and crying; skin—baths and massage). The impulses may be repressed so that symptoms appear when the tension disturbs organ function. Of course oral as well as dermal and respiratory trends can exist in the same individual. But Saul states that it is the person in whom the dermal and/or respiratory mechanism has some weakness, or is a point of fixation, or in whom the attachment to the mother predominately takes these forms, who seems to be predisposed to skin and respiratory allergy.

He concludes—"the dermal and respiratory mechanisms, trends, and relations to the mother are analogous to the oral ones. They are fundamental to an understanding of psychobiological functioning. Preliminary observations strongly suggest that they play a role in the skin and respiratory allergies similar to that of the oral ones in the gastrointestinal disorders."

While we cannot delimit constitutional and acquired factors in the genesis of these disorders I think we can distinguish between the physical (allergic) and psychological factors that enter into the problems. Indeed it is essential for proper management.

A recent coöperative effort at treatment by an allergist (Miller) and psychotherapist (Baruch)²³ dealt with twenty-two patients, seven of whom were children. In all cases the history of classical allergic symptoms was confirmed by positive skin reactions to various allergens. Aware that clinical allergy must be practiced with constant awareness that psychogenic factors influence physical results, the authors utilized individual and group psychotherapy in dealing with their patients. Repeatedly they observed that the fluctuation of symptoms paralleled the degree of freedom with which a patient expressed his feelings and that the intellectual appreciation of the dynamics involved was not important to the patient. Marked improvement was observed in nineteen of the twenty-two allergic patients. They feel that allergic symptoms express hostility, mask a feeling of guilt or anxiety, and at the same time represent attempts to gain sympathy.

SUMMARY AND CONCLUSIONS

The allergic and the neurotic populations are so large that they must overlap. If for no other reason, therefore, these disorders will exist in the same individual. But, in addition, personality studies suggest a more intimate connection—a specific relationship between neurotic character structure and allergic disorder—possibly representing parallel manifestations of the same basic fault, the one discharging on the level of psychic representation through thoughts and feelings and the other on the physiological level by means of disturbances in organ functioning.

Psychosomatic study of an allergic problem, therefore, utilizes separate techniques—psychological and physiological—applied simultaneously; and diagnosis must be established not simply by exclusion or evaluation of physical factors but with additional positive evidence of personality disorder meeting certain psychosomatic postulates. This will demonstrate that in a given case physical and psychological factors act in a complementary fashion to produce the disorder—in one instance specific physical factors may predominate, in another instance specific emotional factors. The latter seem to be determined by certain trends within the personality—just as oral attachments seem to determine

gastrointestinal disorders so do respiratory and dermal attachments (to the mother) apparently determine respiratory and dermal allergic manifestations (Saul).

Migraine seems more closely related to the character structure and personality trends observed in patients with essential hypertension, having to do with the amount and disposition of hostile impulses.

The allergic disorders seem to fall for the most part into the group of organ neuroses that can be termed vegetative (Alexander), representing early and profound deviations of personality development. What role the constitution may play cannot be determined—no methods are available to delimit constitutional and acquired factors. One can, however, evaluate physical and psychological factors and proper management depends on such evaluation. Then psychotherapy plus the allergic approach will mean better treatment for the individual with an allergic disorder.

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THE EFFECT OF TRAUMA AND STRAIN ON THE PRODUCTION AND AGGRAVATION OF HEART DISEASE*

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THE world is at present recovering from its greatest traumatic experience. This, perhaps, justifies a reëxamination and review of the knowledge of the effects of trauma and strain on the circulation, the more so since the war has produced new observations in this field. In recent years the subject has often been debated in the manner of a dispute with legalistic implications rather than objectively. This is inevitable where scientific proof is lacking and the possibilities of litigious heart disease are present, as in personal injury, industrial accident, and compensation cases.

Trauma is defined as an injury or wound. Such injury may vary from the damage of such shocking disasters as airplane crashes and atomic bombing to the minor entanglements of automobile fenders or the malign effects of overeating. But also this concept of trauma includes such influences as the inhalation of toxic gases and psychic injury without physical impact.

Strain, similarly, may be of short or long duration, severe, mild, usual or unusual, physical or mental.

In general, one may conclude that, in the category of harmful influences we are considering, the injury is so produced that some person, external agent, or set of circumstances to which the victim was forced to react, could be held responsible, responsible in a causative, not a legal, sense. This is in contrast with the effects of bacteria, metabolic products, or neoplastic or degenerative processes.

The literature on the subject has become extensive. One need mention only the reviews of Bright and Beck,¹ Master and his associates,² Boas,³ Willius,⁴ Sigler,⁵ Barber,⁶ Riseman and Smith,⁷ Arenberg,⁸ Gilbert,⁹ Parsonnet and Bernstein,¹⁰ French and Dock,¹¹ Blumgart,¹² Pater-

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son,¹³ Brahdry and Kahn,¹⁴ Fitzhugh and Hamilton,¹⁵ and White and Glendy.¹⁶ At least seventy-five pertinent references may be found in the past six years.

The war has drawn attention to such syndromes as the effect of blast concussion, airplane accidents, and fatal coronary artery disease in young men. Autopsy correlation has been of convincing value. None of us who has served in the Army or Navy can retain a dogmatism about the subject based on civilian experience alone.

Types of injury. It is customary to divide the types of injury to the heart due to trauma and strain into (1) Direct penetrating. (2) Direct non-penetrating. (3) Remote injury to other parts of the body or the effects of unusual physical exertion. (4) Psychic injury.

Only the first two may ordinarily injure a normal heart, but a severe general injury may rupture the heart, and strenuous physical effort may rupture a normal aortic valve or normal chordae tendineae of the mitral valve. That all of these injuries may aggravate a preëxisting cardiac disease may be admitted. Only long experience and a judicial mind can allocate the degree of damage due to the chronic process and the added disability attributable to the injury. Furthermore, the probabilities of injury and the type of injury due to trauma or strain will vary with etiologic type of the underlying heart disease. Aortic aneurysm, for example, would be liable to a rupture from strain, whereas auricular fibrillation would be more likely to ensue with mitral stenosis.

While interesting data from combat experience in this war have been added to our knowledge of *direct penetrating injury* of the heart the mechanisms are simple and obvious and will not be discussed here. Recovery with foreign bodies in the heart wall may be miraculous. The escape of the heart from injury may also be surprising. The author saw in consultation some thirty-five patients, aboard a hospital ship off Tarawa, who had been shot through the chest, with foreign bodies often lodging in the lung or mediastinum, without cardiac injury. An obvious conclusion would be that those shot through the heart or great vessels did not reach the ship.

Direct, non-penetrating, non-fatal injuries of the heart are probably commoner than previously thought by most observers. The work of Beck and others has emphasized the syndrome of the "steering wheel" injury with compression of the heart.

Arenberg noted that, in two hundred and fifty cases of non-pene-

trating chest injuries, the worst effects were in subjects with elastic chest walls, and that more damage occurred in those without rib fractures. This confirmed Sigler's⁵ findings that the factors influencing the effects of trauma to the heart were (1) the flexibility of the chest, (2) the presence of underlying coronary disease, and (3) the psychoneurotic tendency or vagosympathetic imbalance of the individual.

In severe blows to the chest or in cases where the patient falls striking the thorax, it may be difficult to localize the area of the trauma. Butterworth and Poindexter,¹⁷ however, found that the chest blows received by thirty-five Golden Gloves boxers produced no significant electrocardiographic changes in tracings recorded directly before and after the bouts. This would seem consistent with the age and normal cardiac condition of the contestants and the degree of trauma. What might happen to previously damaged hearts might well be different. We have seen one boxer, a negro, who developed tuberculous pericarditis following a precordial blow. Such a case belongs in the field of trauma and tuberculosis, rather than trauma and cardiac disease.

Certainly minor myocardial contusions may occur with relatively insignificant chest injuries, but, for proof, one must demand definite clinical signs or significant electrocardiographic changes returning to normal with recovery. What are significant electrocardiographic changes should be interpreted with extreme caution and appreciation of the normal variants of ST and T segments, especially in lead III and the chest leads, related to change of position, anoxia, and emotion. T wave inversion in leads I and II or ST segment displacements of over 2 mm. or intraventricular or A-V block are evidence of myocardial damage.

It is my opinion that failure to diagnose an occasional, slight myocardial contusion is an error more justifiable than the apprehensive opinion that minor electrocardiographic changes and effort syndrome symptoms commonly mean cardiac damage, with the resultant fixation of cardiac neurosis.

It is clear that each case must be individualized, but in the normal heart non-penetrating, non-fatal, non-shocking chest trauma may cause the following conditions: 1) Pericarditis—tuberculous, acute fibrinous, serous or hemorrhagic, or rupture of the pericardium. 2) Heart block—auriculo-ventricular, intraventricular (?). 3) Abnormal rhythms—premature beats, auricular paroxysmal tachycardia, auricular flutter, auricular fibrillation and possibly ventricular fibrillation. 4) T wave and ST

segment abnormalities. 5) Ruptured aortic valve or detachment of chordae tendineae. 6) Congestive failure from myocardial contusion; myocardial laceration with immediate or delayed rupture. 7) Angina pectoris. 8) Coronary occlusion.

Remote trauma, not producing shock, or sudden severe exertion, appears effective in these conditions: 1) Subacute bacterial endocarditis from dental extraction or from an injury which disturbs the immunity process. 2) Rheumatic fever may rarely be reactivated by an injury or surgical operation. 3) Auricular fibrillation may be induced by severe effort, injury, or electric shock. 4) Ventricular tachycardia may be produced by inhalation of chlorinated hydrocarbons—tetrachlorethylene, carbon tetrachloride, chloroform, ethyl chloride, and cyclopropane.¹⁸ 5) The anoxia of carbon monoxide inhalation may produce myocardial necrosis and precipitate anginal or congestive failure in those with coronary artery disease. 6) Normal heart valves may be ruptured by exertion such as cranking a car, and normal chordae by an effort like rowing. Other coronary effects will be considered later.

Since these conditions have been observed and reported with adequate necropsy study, it should lead us to consider the possibility of such cardiac injury in all traumatic cases. Moreover, such patients should be kept under observation for at least two weeks with the realization that in a rare case the final effects of trauma may not appear for weeks or months, as in post-traumatic adhesive pericarditis.

The minimal evidence for injury to the heart when not otherwise explained should be one or more of these findings: 1) significant electrocardiographic changes, 2) cardiac enlargement unexplained by pre-existent cardiac disease or hypertension, 3) abnormal rhythms, not including premature beats unless supported by other electrocardiographic changes, 4) pericardial friction rub or cardiac tamponade, 5) aortic diastolic or loud mitral systolic murmurs with signs of congestive failure, 6) congestive failure immediately precipitated by trauma or strain, 7) angina pectoris or myocardial infarction starting within twenty-four hours of the trauma if accompanied by distress at the time of the incident. If the injury is severe, such conditions starting at any time during convalescence can reasonably be attributed to the traumatic event.

Rarely, cardiac damage eventually fatal may not reveal itself for several hours, or even days, and in the interim the individual goes about

his business without disabling symptoms. Such has occurred in myocardial contusion leading to delayed rupture.

I have reserved for more detailed consideration the most troublesome relationship in this field, that between *coronary artery disease and trauma or strain*.

It is a peculiar fact that most everyone will agree that a man with coronary artery disease may die from sudden exertion, but there appear to be two schools of thought when doctors consider those who do not quite die from myocardial infarction accompanying or following exertion. One group believes that coronary occlusion arrives unrelated to any outside influence in the relentless process of coronary narrowing from atheroma. The other school is ever on the alert to discover in the patient's history some unusual exertion or strain which precipitated the occlusion. There is, it is true, an intermediate point of view which holds that myocardial infarction of lesser degree, subendocardial in situation, is produced by the relative ischemia of a reduced coronary flow in an atherosclerotic vessel plus added myocardial demands, the syndrome of coronary insufficiency.

Statistics have been published to show that coronary occlusion bears no relationship to effort, trauma, strain, or occupation, since no more attacks occur during the active hours of the day than would be proportionately predicted, and that many attacks occur at rest or during sleep. Other figures, while admitting the frequency of coronary occlusion during inactivity, point out that this does not preclude the possibility that a given unusual exertion may precipitate such an occlusion prematurely.

These differences are not based on a confusion of terminology since it is recognized that coronary occlusion, if slowly produced, may not cause myocardial infarction, and that conversely, infarction of the myocardium may occur from coronary insufficiency without occlusion.

The main dispute surrounds the analysis of a typical case of a patient with acute myocardial infarction with characteristic electrocardiographic changes, and survival, who had engaged in an unusual effort, or been subjected to unusual strain, directly preceding the onset of his attack. Was the attack fortuitous and coincidental or causally related to the stimulus?

Let us consider the mechanisms suggested by different authors for the production of myocardial infarct, with or without coronary occlu-

sion. Let us, furthermore, grant that underlying coronary disease is always present in these cases of myocardial infarction excepting the extremely rare direct injury to a traumatized coronary artery. In all these mechanisms a relative, or absolute, ischemia and anoxia of the heart muscle is produced.

I. *Lowered coronary blood pressure and reduced coronary flow resulting in thrombosis.* (a) Normal resting pressure for the given subject during sleep. (b) Reduced systemic blood pressure in shock. (c) Abnormal cardiac rhythms—tachycardia or bradycardia. (d) Reduced blood pressure by hemorrhage. (e) Lowered blood pressure occurring after exertion. (f) Lowered blood pressure in dehydration. (g) The reduction of cardiac output during forced expiration of effort, with closed glottis (Valsalva effect), producing coronary insufficiency.¹⁹

II. *Elevated coronary pressure.* (a) A rise in blood pressure from exertion, pain, or emotion results in rupture of abnormal intimal capillaries in the coronary walls. This may be favored by local anoxic effects with softening of atheromatous deposits beneath the intima. The hemorrhage may rapidly or slowly produce a subintimal projection impinging upon the opposite wall of the coronary vessel occluding the lumen, or it may rupture into the coronary vessel furnishing a raw surface for the deposition of thrombus. (b) A similar rise in blood pressure may rupture an atheromatous abscess through the intima and dislodge an atherosclerotic plaque or the contents of the abscess as material for distal occlusion of the vessel, or also produce a raw surface as a base for thrombus formation.

III. *Miscellaneous mechanisms of anoxia.* (a) Reflex coronary spasm, especially the gastro-coronary reflex occurring after meals or with hiatus hernia, gall bladder disease and other intestinal pathology. (b) The relative ischemia of effort whereby the coronary supply is inadequate to prevent myocardial necrosis in the presence of increased demands. (c) The anoxemia of anemia. (d) The anoxemia of carbon monoxide poisoning. (e) Chronic excitement of the vagus (recently disproved). (f) Inhibition of sympathetic tone as occurs in experimental animals by stimulation of the nasal mucous membrane and may occur in man by the inhalation of cold air.⁹

IV. *Other possible mechanisms.* (a) Direct mechanical injury of a coronary artery, causing spasm or hemorrhage. (b) Vitamin deficiency. (c) The effect of trauma is more severe in experimental animals under

the influence of digitalis, thyroxin, or epinephrin.

With all these possibilities one might feel indeed that any condition which disturbs the "steady state" of a person with coronary artery disease might precipitate coronary insufficiency or even coronary occlusion. How often any one of these is effective cannot be told, cannot even be suspected without much more autopsy study, nor will that answer the question of just what happens in those who survive myocardial infarction. Why then should we not be content to fall back on an appeal to coincidence, since all we can ever say is that it "might" have happened thus and so in a given case, but we cannot prove in this case that it "did" happen in this fashion?

One day last December the driver of a pick-up truck stalled his car in a snowdrift in Boston. Two men offered to push him out and one of these three men died. It seemed like a clear case of unusual physical exertion and latent coronary disease. But the man who died was the driver sitting behind the wheel of his truck and not one of the men pushing it. Was this coincidence or could we discover that the driver actually had tried to shovel the car out, that he had wrestled with the gears and steering wheel, or that the cold and the excitement of the episode were actually factors in his death? Until the whole story of such a case is known in finest detail, should we attempt a surmise? Thus it is of value to study the antecedent activities, the actual effort or strain, and the resulting condition of every patient with myocardial infarct.

In 1933 Fitzhugh and Hamilton¹⁵ became convinced that acute coronary closure and fatal angina pectoris might be deferred in patients with known coronary disease if attention was paid to warning such patients to avoid "departures from ordinary living" or what, to borrow a term of biophysics, I have called a "steady state." They collected one hundred cases in which the following conditions appeared operative in precipitating the occlusion, or what Chief Justice Rugg called "acceleration of previously existing heart disease to a mortal end sooner than otherwise it would have come," which, incidentally, is a crucial phrase. (1) Prolonged activity and fatigue. (2) Persistence in activities that had repeatedly caused angina. (3) Travel. (4) Emotional strain. (5) Alcoholic excess. (6) Starving. (7) Medication, thyroid and bromides. (8) Sexual excess. (9) Straining at stool. (10) Gorging.

Other activities associated with myocardial infarction, including those reported by Boas are: (1) During heart failure. (2) With shock.

(3) With pulmonary embolism. (4) Acute hemorrhage. (5) Acute infection. (6) Marked tachycardia or bradycardia. (7) Hypertensive crises. (8) Chest injury. (9) Exertion—sudden, severe. (10) Allergy. (11) Cold. (12) Insulin shock and hypoglycemia. (13) Electric shock. (14) Excessive heat and humidity.

A patient in this category whom I recently examined was a sailor in his early thirties who arose one afternoon feeling well, shaved, and went to breakfast. He was suddenly stricken by the sensation of a blow in the mid-sternum as if "a man had hit me and pulled his arm away and left his fist in my chest." He survived a typical myocardial infarction. Prior to this attack he was free from all symptoms, but it appeared that he was on two weeks leave and had been drinking heavily during this time, accounting for his afternoon breakfast. In spite of what some may think this is "a departure from ordinary living" in the Navy.

Although one may remain sceptical of the causal relationship in some reported cases, the experience of World War II shows that subjecting men to exertion to which they are unaccustomed and *which they must perform in the face of severe fatigue*, has precipitated coronary failure, occlusion, and sudden death.

The reports of French and Dock¹¹ and of Blumgart¹² are very convincing. In the former series vigorous effort and early morning chores were the apparent cause in over fifty per cent of eight fatal cases of uncomplicated coronary disease.

In Blumgart's series of eleven cases, 30-56 years old, effort was considered the precipitant. His conclusions are notably sound: "The relationship of effort to a given attack of coronary occlusion may be certain, probable, suggestive, or improbable, or non-existent. The relation is definite if these criteria are satisfied: (1) The development and increase of cardiac symptoms such as pain or substernal distress during or immediately following unusual effort. (2) The continuation of the symptoms after cessation of effort. (3) The presence of the clinical signs and symptoms of acute myocardial infarction. (4) The development of the characteristic electrocardiographic patterns of acute anterior, posterior, or lateral wall myocardial infarction."

In 1941 Westinghouse and I²⁰ reported seventy-seven attacks of sudden occlusion of peripheral arteries, including the retinal arteries, by the mechanisms of embolism, thrombosis, and endarteritis in ambulatory, apparently well, individuals. These occlusions occurred four-

teen times as commonly when the person was at complete rest than when engaged in the ordinary exertions of life.

I confess that the situation in the peripheral arteries may be different from that in the heart, but it does seem as if a relatively reduced blood flow was more conducive to thrombosis than a very active one. However, a very few of these episodes occurred during severe exertion.

Willius,⁴ however, has gone the whole way in one direction. Since, as he says, coronary thrombosis never occurs in a normal artery, strains in the past in the case of the afflicted individual did not produce occlusion, which occurs more often in the sedentary and at rest, then effort bears no relationship to coronary thrombosis. From a compensation viewpoint based on the emphasis on a precipitating event, he says, "The practice of genteel extortion has become so widespread as to constitute an alarming scheme of sanctioned fraudulence."

This, I feel, is a limited peacetime attitude, and too selective, but also too often it is true.

It is quite obvious that the restraining influence against soft-heartedness on our part in compensation cases is the possibility of malingering or traumatic neurosis. For that reason the symptoms of precordial pain, dizziness, faintness, sweating, sighing, and palpitation cannot be accepted alone as showing injury to the heart. Let the defense be psychiatric and not cardiologic.

But by all means let us be objective to the extent of refusing categorical answers. Let us emulate Dr. Jelley on the witness stand. He was once presented by the lawyer with the longest hypothetical question on record.²¹ It was twenty thousand words and took three hours to deliver. At the end of it Dr. Jelley's answer was, "I don't know."

No matter how hard we try the legal methods may defeat our best intentions. Though we may see no relationship between a given incident and the aggravation of preëxisting cardiac disease, a lawyer may confound one by replying "then you think it is good for a man with heart disease to fall down on an icy sidewalk?"

There remains consideration of *emotional trauma*. In the main it is a good legal principle that nervous strain cannot be considered a compensable injury if the emotional trauma was of such a sort as not to be expected to harm a normal individual. Otherwise might we not all be liable for fatally irritating a man with angina?

Emotion may speed the heart and raise the blood pressure, but while

the released adrenalin acts as a coronary dilator, this beneficial effect may be negated, in the individual with coronary narrowing, by the concomitant increase in cardiac work due to the emotional discharge. Pain, induced by constriction of a limb or the cranium, will produce changes in the electrocardiogram in subjects with coronary disease.²² The T waves may increase or decrease in amplitude, an abnormal tracing become normal, and vice versa. Occasionally this appears to be true in normal subjects.

These findings are difficult to evaluate, but show that something does take place in the coronary circuit under painful stimuli usually with increase in blood pressure, but just how this is mediated is not clear. Graybiel has shown that the startle reaction produced by firing a gun behind a normal subject can cause, in the electrocardiogram, bundle branch block, inverted T waves, and displacement of the pacemaker. One should, therefore, be reluctant to interpret too much significance into electrocardiograms purporting to indicate coronary injury from emotional stress.

The delayed appearance of myocardial infarction following a single emotional strain would seem highly unlikely. But the control of emotions may well prolong the life of a person suffering from coronary disease. One of Hamilton's patients, "a gentleman of the old school, famed for his easily aroused ire, found at the age of seventy that indulgence in bad temper caused him angina. He succeeded completely in controlling his disposition and lived for ten years in a forced good humor."

The cardiac responses effecting sudden death from exertion or emotion are not all known. Ventricular fibrillation or standstill appear to be two of them. It is hardest of all to prove the mechanism of unexpected death in apparently normal young individuals with normal hearts at necropsy.

Raab²³ has reported the autopsy findings in a young man who died during a game in whom there was a very high concentration of epinephrin bodies in the heart muscle as the only abnormal finding.

One of my pathologist friends said recently that there is no reason why a normal person could not faint to death if he were propped up during syncope. Such seems to have occurred in an exhausted soldier who returned from the battlefield, ate a heavy meal, and fell asleep in sitting position against a wall.

Finally, from a practical experience in industry what may one conclude about the *danger of employing men with latent coronary disease*? I will quote only one such report. In twenty years the Eastman Kodak Company has had only one case of a death claim for aggravation of existing heart disease. At autopsy this man was found to have a syphilitic aorta with a moderate back strain as the cause of the claim.

One hundred employees died of coronary thrombosis in the years 1921-1940. In only twelve did symptoms begin at work and in only one case was there a question of aggravation by work activity. Crain,²⁴ who reports this experience, states that a good preemployment physical examination defining the disability is as good as a waiver of disability in cases of compensation.

In *summary* let me emphasize what seems necessary to further the study of this ramified subject of trauma and the heart. The desiderata in every case are these: (1) An honest history, taken as soon as feasible after the event. (2) The absence of present or impending litigation. (3) The condition of the patient prior to trauma or strain. (4) The antecedent activities of the patient for at least a week before. (5) The customary physical and emotional habits of the subject. (6) The exact degree of injury or strain. (7) The history immediately after the episode. (8) The bridging of symptoms or "intercalary period." (9) The departure of the patient from his normal equilibrium following the episode. (10) The objective evidence of cardiac injury—change in heart size or function, pericardial or endocardial variants, electrocardiograms. (11) The assessment of the neurotic component. (12) The autopsy findings or the final recovery state.

Numerically, after all, this group of cases is a small part of cardiology. I do not wish to over-accent the role of trauma or strain in the production or aggravation of heart disease, since such are the exceptional and not the usual factors. Infection is vastly more important.

But, in all cases, let me plead for an open mind, full experience, and the rule of reason. This should not be a battle of conflicting authorities in which "God fights on the side of the heaviest artillery" unless such artillery be the truth, as we know it, and not as we imagine it.

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THE EXTRA-RENAL SEQUEL TO
EXPERIMENTAL RENAL HYPERTENSION*

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THE recently revived interest in the study of experimental hypertension has been largely directed toward understanding the etiology of hypertension as seen in man, especially essential hypertension, and toward producing this disease experimentally for further study. Although neither of these intentions has been crowned with direct success, our understanding of the circulation, both normal and hypertensive, has been greatly increased by these studies, and particularly those initiated by Goldblatt's¹ work on clamping the renal artery. So it seems worthwhile to consider experimental hypertension as a field of study in itself and to review some of the observations in an attempt to evaluate changing concepts in the field.

EXPERIMENTAL HYPERTENSION OF CEREBRAL ORIGIN

Since the cerebral cortex is dependent upon an immediate blood supply, and the carotid and vertebral arterial systems seem specially designed to guard it, one might expect that an interference with the proper delivery of blood to the brain would produce a compensatory rise in blood pressure. That this is not a simple arrangement is clear since intracranial vascular disease usually does not produce chronic arterial hypertension unless there is an accompanying change in intracranial pressure.

This question has been approached experimentally by Nowak and his colleagues² who found that successive ligation of the various cerebral arteries is sometimes followed by chronic hypertension, but Blalock and Levy³ produced only temporary hypertension by this means.

Dixon and Heller⁴ using dogs, and Griffith, Jeffers and Lindauer⁵ using rats, produced sustained hypertension by raising the intracranial pressure by the intracisternal injection of kaolin. Griffith and Roberts⁶

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found about four-fifths of rats or dogs so injected became hypertensive. The inflammatory reaction and leukocytosis resulting from these injections had usually begun to subside before the hypertension appeared. This observation is in contrast to the prompt rise of blood pressure which occurs in man as the intracranial pressure rises. Reports indicate somewhat variable results with this method; Blalock in his review⁷ expresses the belief "that this type of hypertension cannot be produced with great regularity and that the elevation of blood pressure is usually not persistent." At the present time it may be said that there is no clear indication that studies of cerebral ischemia by arterial ligation or the injection of kaolin have shed much light on the etiology of human hypertension except that which follows injuries, tumors, and other causes of raised intracranial pressure. Nor has there been a sufficiently varied or extensive study made of animals hypertensive from these causes to add considerably to our knowledge of the behavior of organisms as a whole, or of various organs within them, when subjected to a period of raised blood pressure.

At this time a careful experimental study of cerebrospinal fluid pressure in animals with Goldblatt hypertension might be fruitful.

HYPERTENSION FROM VITAMIN D AND DESOXYCORTICOSTERONE

The association of elevated systolic blood pressure with raised blood cholesterol and arteriosclerosis led to the experiments in which Appelrot⁸ studied the possible hypertension-producing effect of Vitamin D₂. The data are insufficient to add much to our knowledge of hypertensive processes; but Handovsky⁹ reports that dogs whose blood pressure was maintained at hypertensive levels for eighty days during administration of Vitamin D₂ did not continue to have hypertension after the drug was discontinued.

The elevation of blood pressure arising from injection of desoxycorticosterone is at present difficult to interpret. Other aspects of the physiology of various steroids of biological importance are at present undergoing intensive study all over the world and it seems likely that the part played by these substances in cardiovascular disturbances will be somewhat clarified shortly.

BUFFER NERVE HYPERTENSION

We may now turn to hypertension produced by experiments on

buffer nerves, some of which are already applicable to our understanding of the hypertensive process.

The study of hypertension produced by denervation of the cardio-aortic and carotid vasosensory zones has been pioneered by Heymans but this method has been used enough in other laboratories so that the essential facts are well known and are matters of fair agreement.

The pressure-sensitive nerve endings in the left ventricle, the arch of the aorta, and the carotid sinus are continuously sending afferent impulses to the medulla tending toward the reflex lowering of blood pressure. Bronk and Stella¹⁰ have shown that each systole produces an increase in the frequency of afferent impulses from these regions and therefore tends to produce a vascular relaxation at the peak of systole. This work shows the rapidity of that reaction, its sensitivity, and the fact that it is normally operating in the pressure ranges which occur in the resting physiological state. The efferent pathways for these depressor effects are widespread but probably include diminution of sympathetically maintained vascular tone particularly in the splanchnic area.

Denervation of these vasosensory zones in acute experiments results in an immediate rise of blood pressure and cardiac acceleration, and Heymans and others have shown this to be largely due to a rise in sympathetic tone.

Chronic hypertension has also been produced by the denervation of these zones. For anatomical reasons the operation is difficult and uncertain particularly since the aortic depressor fibers in most species accompany the vago-sympathetic trunk and are difficult to isolate and divide. Such extensive surgery as that involved in denervating both aortic depressor zones and both carotid depressor zones is commonly attempted in a multi-stage operation. At best the final stage results in such profound cardiovascular disturbances as to endanger life immediately; and accidental interruption of vagus efferent fibers at the site of operation is liable to produce serious disturbances in the respiratory and digestive systems which may kill the animal later.

These reasons may account for the discrepancy between the pupils of Heymans, who after considerable experience are usually able to produce satisfactory chronic hypertension, and others who have commonly produced only moderate and temporary hypertension and so have been inclined to abandon the procedure before acquiring extensive

experience with it.

If the animal with chronic hypertension of this kind is sympathectomized completely, its blood pressure is restored to normal (Heymans¹¹). There is no agreement (Nowak and Walker²) as to whether hypertension develops if the section of the moderator nerves is made originally in a sympathectomized animal. Grimson, Bouckaert and Heymans report¹² three animals in which they first performed splanchnic sympathectomy, complete except that the renal nerve supply was left intact. Next, they raised the sympathetic tone by denervation of the cardio-aortic and carotid zones. In these three animals the rise in blood pressure which ensued was believed to be due to renal vasoconstriction causing renal ischemia and thus hypertension of the Goldblatt type. These animals were later subjected to denervation of the kidneys and the blood pressure returned to normal. This type of study which involves three major operations: splanchnicectomy, moderator nerve section, and renal denervation, and requires repeated blood pressure measurements, is evidently difficult. This is a sufficient justification for the limited number of experiments reported. Unfortunately, in this experiment, the assumption is implied that the mechanism of hypertension once established is not subject to change; and therefore Heymans did not investigate the effect of varying the time interval between the establishment of the hypertension and its "cure" by renal denervation. An assurance that such animals would be cured of their hypertension by renal denervation even after a period of many months' or years' hypertension would be valuable in the consideration of the effects of prolonged elevation of blood pressure on the organism as a whole. This is a point of importance which will be discussed more fully in connection with chronic renal experimental hypertension.

The foregoing discussion of experimental hypertension of non-renal origin serves to indicate some of the lines of approach to the important question: Which of the phenomena of renal hypertension may properly be attributed solely to the change in intra-arterial pressure as contrasted with those effects due specifically to the kidney?

EXPERIMENTAL RENAL HYPERTENSION

The essential facts about experimental renal hypertension are well enough known that they need but the briefest recapitulation here.

Elevation of systolic and diastolic blood pressure may be regularly

produced by partial occlusion of both renal arteries by a Goldblatt clamp¹ or ligature (Wilson and Byrom¹³) or by the production of perinephritis such as can be induced by wrapping the kidney in silk or cellophane (Page¹⁴). Hypertension can also be produced by tightly constricting the kidney with tape according to the technique of Grollman¹⁵ or by partial ablation of kidney tissue as described by Chanutin and Ferris.¹⁶

Hypertension produced by these means may be of rapid onset, rapid progress and lead to death; may be of slower onset and lead to stable chronic hypertension; or may be only temporary. This depends upon the procedure employed, the presence or absence of an intact kidney, the species under observation, and probably a number of other uncertain factors. These methods all produce hypertension but the mechanism is open to discussion and may now be examined.

Mechanism: It is usually believed that in such experiments the kidney liberates renin into the blood stream. This reacts with a part of the globulin fraction of the plasma (renin substrate— α_2 globulin) to form the vasoconstrictor substance, angiotonin, which is directly responsible for the hypertension by raising the peripheral resistance.

What part of the kidney produces the renin, and the mechanism of its liberation is uncertain.

CHANGE OF MECHANISM DURING THE COURSE OF EXPERIMENTAL RENAL HYPERTENSION

Renin may be liberated very promptly in response to emergencies which reduce the pressure^{17, 18, 19} but there is no certainty as to how long the kidney will continue to secrete renin. Probably in extreme circumstances the kidney can be exhausted in a few hours.* It has generally been assumed that the hypertension established by moderate renal artery obstruction and consequent renin liberation may continue indefinitely with no change of mechanism but since we know that renin substrate may be quickly exhausted by the rapid injection of renin or even by causing the kidney to liberate a large amount of this substance, it is becoming increasingly evident that this view must be reexamined critically.

Renin in Circulating Blood: If renin, in fact, is responsible for ex-

* Shorr finds apparent exhaustion of his renal vaso-excitor material in four hours of hemorrhagic shock.

perimental renal hypertension, it should be possible to demonstrate its presence in the circulating blood. Attempts to do this have usually been unsuccessful but some investigators have detected renin in the blood stream of dogs shortly after the application of the clamp (Dell'Oro and Braun-Menendez²⁰) and have remarked upon its apparent absence later.

Fasciolo, Houssay and Taquini^{*21} found renal vein blood from hypertensive dogs to have a raised vasoconstrictor action on the perfused frog. Mason and Rozzell²² were unable to confirm this. This disagreement was abolished when it was realized that the former had used dogs with newly established hypertension, the latter chronically hypertensive dogs.

It has been suggested that the animal may become increasingly sensitive to the pressor action of renin, and that therefore later hypertension might be sustained by immeasurably small amounts, but the experimental evidence does not allow of this being the sole explanation (Pickering²³).

Hypertension from renin infusion²⁴ or from acute and severe limitation of renal vascular supply is of notably small magnitude and short duration and usually lasts only a few hours.

Renin is found during acute glomerulonephritis²⁵ but not in chronic hypertension in man. Pickering²⁶ has adduced other evidence indicating a fundamental difference in the mechanism of hypertension of acute and chronic nephritis.

Dock and Rytand²⁷ demonstrated the absence of vasoconstrictor substances in rats made hypertensive by partial nephrectomy, but they do not say how long the rats had been hypertensive. In view of all the other evidence for the humoral origin of renal hypertension their conclusion offers some support to the idea that more than one mechanism is involved in the course of renal hypertension in the rat.

Dock²⁸ made rabbits hypertensive by renal artery ligation, pithed them under anesthesia and found them to have blood pressures as low as normal animals similarly pithed. Since pithing lowered the blood pressure completely, he concluded that the hypertension was not mediated by a circulating pressor substance, but that the hypertension in these animals was due to a change in the "set" of the central nervous system, comparable, perhaps, with the change of the "set" of the thermal

* Dr. Taquini informs me that this question is now being reinvestigated by Dr. Fasciolo in Buenos Aires with recent improvements of technique. Preliminary correspondence with Dr. Fasciolo suggests that renin is demonstrable in normal and hypertensive animals, but that animals with long-standing hypertension have smaller quantities of renin circulating.

regulatory mechanism in lobar pneumonia.

Probably renin is not operating in rabbits after seven weeks of hypertension, so Dock's rabbits which had been hypertensive for "months" may be considered "chronic." This observation of Dock's that the nervous system is involved in late hypertensive rabbits and that a humoral system is not involved further supports the concept that the mechanism of experimental renal hypertension changes with time.

Pickering²³ showed that rabbits with recently induced renal hypertension have normal sensitivity to injected renin as contrasted with chronic renally hypertensive rabbits whose sensitivity is unusually great and prolonged. (These experiments are complicated by the fact that his observations were all made on animals shortly after complete nephrectomy, which of itself may sensitize to renin.)

Taggart and Drury²⁹ claimed that renal hypertension does not involve renin at all. They worked on rabbits with hypertension of two months' standing (quoted by Pickering) which therefore belonged in the "chronic" category. These rabbits were normally responsive to injected renin and when made tachyphylactic by repeated doses of renin their hypertension was not abolished. This suggests that endogenous renin was not causing their hypertension.

Wakerlin in 1943³⁰ showed that a series of injections of renin would prevent the development of renal hypertension if the injections were continued for some time after clamping the renal artery. Many dogs have been studied by him and others for the possible hypotensive effect of renin injections on hypertensive dogs. The results have been variable and in 1946 Wakerlin was at a loss to explain them.³¹ An examination of his figures shows that renin given prophylactically or in the early stages of hypertension is usually effective, whereas extracts given later are variable and temporary in their effects. His results are compatible with the view that the injected renin uses up all the substrate and makes the animal unresponsive to its own renin and therefore abolishes the reno-humoral mechanism of hypertension. The variable results of injections given later may be, and indeed the published figures suggest that they are, due not to renin but to the temporary non-specific anti-hypertensive effect common to many tissue extracts (Chasis, Goldring, and Smith³²).

The difficulty of an accurate interpretation of these experiments in the light of the dual mechanism hypothesis arises from the fact that the

TABLE I
COLLECTED RESULTS OF NEPHRECTOMY ON EXPERIMENTAL
HYPERTENSION IN RATS

Authors	Method of producing hypertension	Number	Result of nephrectomy		
			No change or a rise	Lowered, but not to nor- mal	Return to nor- mal
Wilson and Byrom	Silver clip ob- structing one renal artery	27	8	9	10
Friedman, Jarman, and Klemperer	Cellophane bag around one kidney	44	3	29	12
Patton, Page, and Ogden	Partial occlu- sion with silk tie of one re- nal artery	47	15	20	12
Totals		118	26	58	24
Per cent			22	49	29

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension, *Surg. Gynec. & Obst.*, 76:493-497, 1943. By permission of Surgery, Gynecology and Obstetrics.

experiments were designed rather for another purpose than to test this hypothesis. Friedman³³ using three dogs of at least 54 days hypertension was unable to reduce the blood pressure by renin injections.

A number of workers (Harrison, Blalock and Mason,³⁴ Prinzmetal and Friedman³⁵) have claimed that the ischemic kidney contains more renin than the normal kidney. Pickering, Prinzmetal and Kelsall³⁶ found this to be true for the newly hypertensive rabbit but not for the rabbit with hypertension of long standing. The change in the renin content of the kidneys and in the sensitivity to injected renin and the fact that renin can sometimes be found in the blood of the early hypertensive animal but not in the animal with long established hypertension, suggest that there is a change of mechanism in the course of hypertension and that this is maintained at first by renin and later in some other way.

The Effect of Nephrectomy on Experimental Hypertension: Renal hypertension may be readily established in the rat by the partial ligation of only one renal artery leaving the other kidney intact. Removal of

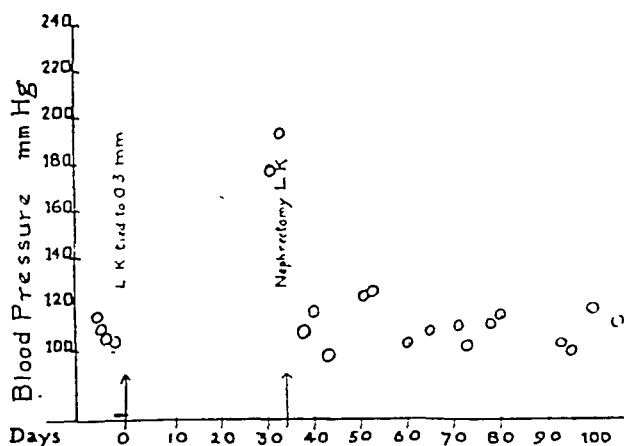


Fig. 1. Complete relief of hypertension of short duration in a rat after removal of the left kidney whose artery had been partially ligated. Right kidney intact.

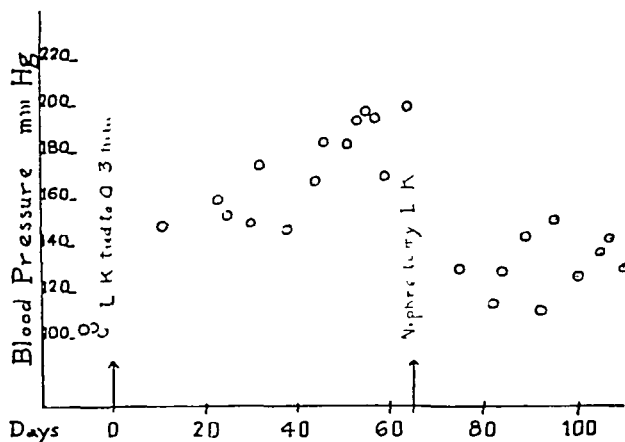


Fig. 2. Moderate improvement after hypertension of 2 months' duration.

the ligated kidney is sometimes followed by a decrease of blood pressure and sometimes not (Table I). Wilson and Byrom¹³ first called attention to this and believed the *degree* of hypertension to be the determining factor.

Friedman, Jarman, and Klemperer³⁷ remarked on the failure of unilateral nephrectomy regularly to restore the original blood pressure in rats hypertensive from silk perinephritis. They also concluded that the restoration depends rather upon the intensity than upon the duration.

We³⁸ reinvestigated the effect of nephrectomy on rats made hyper-

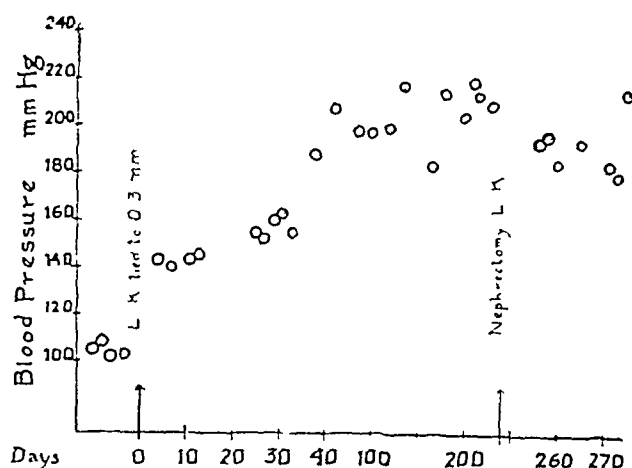


Fig. 3. No lowering of blood pressure after 7 months of hypertension. The time scale is irregular to conserve space.

TABLE II

THE RELATION OF DURATION AND SEVERITY OF HYPERTENSION TO
THE EFFECTIVENESS OF NEPHRECTOMY IN RATS

Duration—wks.	No. of animals	Result of nephrectomy		
		No change or a rise	Lowered, but not to normal	Return to normal
5-10	21	2	9	10
11-45	26	13	11	2
Totals	47	15	20	12
Severity of hyper- tension—mm.				
140-160	26	12	9	5
161-180	11	2	6	3
181-200	7	1	3	3
Over 200	3	—	2	1
Totals	47	15	20	12

(Note that there is no evident relationship between the maximum blood pressure level and recovery.)

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gynec. & Obst., 76:493, 1913. By permission of Surgery, Gynecology and Obstetrics.

tensive by partial ligation of the left renal artery. At various intervals after the hypertension was established, the left kidneys were removed. Figures 1, 2 and 3 are records selected to show that the removal of the affected kidney resulted in more or less lowering of the blood pressure according to the duration of the hypertension. Table II analyzes these experiments with respect to the effect of nephrectomy as related to both the severity and the duration of the hypertension.

These data lead to the conclusion that it is not the degree but the duration of the hypertension that counts and that the longer an animal has been hypertensive from this cause the more likely it is to remain hypertensive after the offending kidney is removed. In these experiments the obstruction of the blood supply to the kidney initiated the hypertension presumably by the renin mechanism; the maintenance of the hypertension, however, must be due to something other than the kidney which has been removed.

In view of the different interpretation of our results from the interpretations of Wilson and Byrom and of Friedman, Jarman and Klempner, it is necessary to seek the cause of the discrepancy. Wilson and Byrom remarked upon the difficulty of interpreting their data because they cannot find a satisfactory figure to report a particular rat's blood pressure during a given period of time and so they have grouped their rats according to their judgment of their behavior. An analysis of the mean blood pressure figures given in their table does not indicate any correlation between the effect of nephrectomy and the intensity or duration of the hypertension, but a study of their grouping shows that of the 18 animals in which nephrectomy cured or substantially improved the hypertension, only three had been hypertensive for more than 10 weeks.

The data of Friedman, Jarman, and Klempner included 44 rats of which only 4 had hypertension of seven weeks or less, fourteen of 7-10 weeks, and twenty-six of more than 10 weeks. Of the four rats with hypertension of seven weeks or less duration three returned so nearly to their original blood pressure levels as to be indistinguishable from normal (*viz.*, 1, 7, 13 mm. above normal) but probably this experiment must be regarded as one in which the number of nephrectomies during acute hypertension is insufficient for discussion in this connection.

It seems that the failure of these two groups to come to the same conclusion as we did with regard to the effect of nephrectomy early in hypertension, may in part depend upon our having used considerably

more rats, namely 21, in the duration group of from five to ten weeks.

The significance of the conclusion that this type of hypertension is initiated by the kidney but maintained by an extra-renal mechanism was not fully realized at the time we published these data. Later, Dr. Sapirstein pointed out to us that this was a key observation in the understanding of renal hypertension, but we were unaware that Pickering²³ had already arrived at the same conclusion on the basis of observations reported by Taggart and Drury²⁹ on the responses to renin of normal and hypertensive rabbits.

Pickering²³ discussed the evidence for the proposition that rabbits during the first week after their renal arteries are constricted have renin hypertension but that later a "non-renal factor" plays an important, and perhaps the chief, role in maintaining the raised pressure. He lists the following three points, and I quote his words:

"In the first week after constricting the renal artery, it has been here shown that the hypertension is usually abolished completely by removing the ischemic kidney. The time taken for the arterial pressure to fall to its normal level is of the same order when the ischemic kidney is removed as it is after stopping an intravenous infusion of renin lasting 4 hours. Finally the renin content of the ischemic kidney is at this stage increased. These facts indicate that the kidney is solely responsible for the hypertension and suggest that the release of renin from the ischemic kidney is the mechanism involved."

Removal of the hypertensive rabbit's kidney after seven weeks of clamping does not abolish the hypertension. He goes on to point out that this concept of a change from a renal to a non-renal mechanism is in harmony with the finding that the newly hypertensive rabbit has a raised renin content in its hypertensogenic kidney whereas the rabbit of longer hypertension does not.

Grollman³⁰ reported that in the rabbit (as in the rat) nephrectomy, after ten weeks of hypertension due to renal compression, does not abolish the hypertension.

In the dog there are no large series of experiments from which one can determine whether the duration of hypertension influences the remedial value of nephrectomy. In general, by selecting from the reported experiments those in which the duration of the hypertension is reported, one may conclude that removal of the kidney causing hypertension during the first month usually abolishes the hypertension.

If the kidney is removed at three months or later, the hypertension usually persists, but before accepting this evidence as a significant differentiation between acute and chronic hypertension in the dog one must consider carefully one well-documented experiment illustrated in Goldblatt's report.⁴⁰ This experiment shows that one dog with unilateral renal hypertension of nine months' duration was completely cured of its hypertension by ipsilateral nephrectomy. The evidence in this instance seems clear cut and the importance of this experiment is so great that it seems unfortunate that only one such animal was available and that so little time was allowed to guard against spontaneous reappearance of its hypertension.

Verney and Vogt⁴¹ give data on two hypertensive dogs nephrectomized on the 15th and 20th days respectively which shows an immediate return of blood pressure to the original level. The authors speak of an additional 4 dogs which behaved similarly but do not give the data. There seems to be little doubt from these experiments and from those of several others (Blalock and Levy,⁴² Rodbard and Katz,⁴³ and Goldblatt⁴⁰) (Rodbard and Katz 6 animals from 5-28 days) that removal of the kidney from a unilaterally hypertensive dog abolishes the hypertension if the nephrectomy is done within the first few weeks.

These studies on nephrectomy in dogs, rats, and rabbits indicate clearly that renal hypertension is dependent upon the kidney only in its early stages but is later maintained by some other means.

The Role of the Nervous System: At Sapirstein's suggestion we (Reed, Sapirstein, Southard and Ogden⁴⁴ and Sapirstein and Reed⁴⁵) gave rats during the early weeks of renal hypertension Nembutal, yohimbine or F883 with no effect upon their hypertension; but animals which had been hypertensive for a number of months usually showed a lowering of their blood pressure in response to these drugs. This suggests that the mechanism maintaining the later stages of hypertension involves the nervous system, particularly the sympathetic system, and that this nervous mechanism is not operating in early hypertension. The experiments of Dock and Dock and Rytand which demonstrate that pithing completely abolishes renal hypertension falls in with this suggestion.

Jacobs and Yonkman⁴⁶ gave yohimbine to four dogs hypertensive from silk perinephritis. The administration of the drug was started fifty to seventy days postoperatively about three to four weeks after

the hypertension was established. In one of these there was an unequivocal fall of blood pressure; in two more a fall was recorded but was so small as to leave its significance in doubt; in the fourth dog no change occurred. The dog whose blood pressure fell with certainty received its medication for twice as long as the dog which showed no change, and even so neither this nor any of the four showed blood pressure restored to the preoperative level. The method of administration of the drug, the species of animal and other differences, make these experiments difficult to compare with those of Reed, Sapirstein, Southard and Ogden, but Jacobs and Yonkman's results might be summarized thus:—administration of yohimbine to newly hypertensive dogs did not consistently lower the blood pressure and never abolished the hypertension. Stated in this form they confirm the observations of Reed, Sapirstein, Southard and Ogden on rats, but the distinction between "newly" and "chronically" hypertensive dogs cannot be made from Yonkman's data though it may be cautiously inferred from other observations and from the life-span of dogs. The concept that dogs of two months' hypertension are nearing or in the "chronic" category would fit in with the work of Friedman.³⁷

The Effect of Sympathectomy on Experimental Hypertension: The experiments just described with Nembutal, yohimbine and F883 suggest that the extra-renal mechanism may be concerned with the sympathetic nervous system. If this is so sympathectomy performed early in the disease might be expected to be without effect whereas it might be expected to restore the blood pressure to its normal levels if performed after renin activity had ceased.

Sympathectomy on dogs with renal hypertension fails to restore the blood pressure to normal values. Generally, the duration of the hypertension before the performance of sympathectomy has not been stated, but where this information is available the sympathectomy has been performed early in the course of hypertension at a time when its failure to affect the disease is to be expected by comparison with the failure of sympatholytic drugs to cure experimental hypertension in rats. Heymans¹¹ removed the sympathetic nervous system with the exception of the innervation to the kidneys, raised the sympathetic tone by moderator nerve section and observed hypertension due to the vascular clamping of the renal arteries. In these dogs the kidneys were denervated six weeks later and the blood pressure was markedly lowered. This indi-

cates that at that time renin was solely responsible for the hypertension and that the nervous system was not participating except by producing renal vasoconstriction.

Verney and Vogt⁴¹ by compression of the renal arteries in six dogs previously sympathectomized recorded moderate to great rises in blood pressure in every case. In one of their dogs the preoperative blood pressure was 116. It rose to a peak of 142 on the 48th day after renal artery compression and had declined to 122 by the 90th day. In another dog the pressures were preoperative 105, 46th day, 170. These dogs are the two dogs followed for the longest time according to their published data and therefore suggest that in the absence of the sympathetic nervous system hypertension of renal artery origin does not persist beyond the third month.

A number of sympathectomies have been performed in hypertensive men but the data from these do not appear to be useful for this discussion for the following reasons:

First, there are many who doubt if hypertension of the Goldblatt type commonly occurs in man and none of the few human hypertensives whose disease seems clearly to be due to this mechanism have been subjected to sympathectomy.

Second, it is rarely possible to say with any certainty how long hypertension has existed in an individual coming up for sympathectomy; probably it is always more than the period corresponding to the few weeks we have been considering in animals.

Third, many of the series of sympathectomies in man are inadequately controlled both with respect to the careful evaluation of the effects of other therapeutic measures upon the blood pressure and with respect to adequate follow-up data.

For these reasons it seems best at the present time not to attempt to analyze and evaluate the various successful and unsuccessful sympathectomies reported with regard to their bearing on this hypothesis. Undoubtedly the recent practical interest in therapeutic sympathectomy will lead to the publication of series in which the data are adequate for use and in which follow-up information can later be effectively collected.

Similarly the facts that Gregory⁴⁷ lowered the blood pressure of hypertensive patients by means of spinal anesthesia and that he demonstrated the absence of effective renal pressor activity in his hypertensive

patients must be interpreted with caution until we can be sure whether these phenomena are true throughout the course of hypertension or if not at what stages they are present.

The effects of sympathectomy, the change in response to drugs, the change in the response to nephrectomy, the change in the sensitivity to injected renin, the change in the renin content in the kidney, and the change in the findings on testing for renin in circulating blood are six basic evidences which may now be put together to offer a tentative story of the dual pathogenesis of experimental renal hypertension.

Dual Mechanism Stated: The application of the clamp, probably by diminishing the pulsatile expansion of the kidney causes the liberation of renin and elevates the blood pressure. This raised blood pressure brings into play an extra-renal (neurogenically operated and sympathetically mediated) mechanism which maintains the vasoconstriction. The liberation of renin ceases either because the general change in vascular dynamics starts the kidney moving again or else by some other adaptation or exhaustion of the renin mechanism. The cause for the cessation of renin liberation is unknown, but the important fact which must be realized is the existence of this very fundamental change in the mechanism of hypertension.

Many experiments would have yielded much more valuable information had this change of mechanism been taken into account in planning the experiments or had the exact intervals between the establishment of hypertension and subsequent experiments on the animal been routinely reported.

The present state of the hypothesis discussed is that no critical experimental data or series of clinical observations are incompatible with this theory as applied to hypertension of the Goldblatt type, but that the critical data to support it are insufficient and are based in part on rats, which are suspect. Many scattered observations point toward the correctness of this view but critical surgical and pharmacological experiments must be performed on dogs and other species before it can be regarded as established.

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TREATMENT OF ACUTE ANTERIOR POLIOMYELITIS WITH CURARE AND INTENSIVE PHYSICAL THERAPY*

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INTRODUCTION

A YEAR has passed since the first complete report was made at the Orthopedic Section of the New York State Medical Society¹ of a method of treating acute anterior poliomyelitis from the onset of the disease, with curare and intensive physical therapy. Therefore it is fitting that another report be made on the second year's experience with this method of treatment. This is the first complete year's experience with the method as an entity. The first report included much developmental work. In treating the patients seen in 1946, the regimen² which was described last year was followed meticulously. The results have been most gratifying.

STATISTICS

Fifty-two patients were treated from June 1, 1946 through April 1, 1947. There were three deaths. This is a mortality rate of 6 per cent. One of these was a fulminating Landry's type ascending paralysis. The other two died with what our pathologist described as acute pulmonary edema. This is probably of the neurogenic type as described by Henneman.³ There are three fair results or 6 per cent. One is a patient who had a total quadriplegia with paralyzed abdominal muscles. There were numerous other factors in this patient, but her diagnosis finally was established as acute anterior poliomyelitis. She has recovered the use of her upper extremities and is beginning to show myographic evidence of power in her lower extremities. Her abdominal musculature is recovering nicely. The other two have major paralysis of muscles controlling one or more joints. It is to be noted here that the criterion

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on which results are based is the evaluation of muscle power, *NOT* functional ability. The vagaries of estimating muscle power are great enough. When function is used as the criterion, the margin of error is too great to allow dispassionate evaluation. One patient, or 2 per cent, is classified as good. She has no total paralysis and only moderate involvement of the anterior and middle deltoid. She had had a total paralysis of that extremity. There are four patients or 8 per cent classified as very good results. These have minor pareses that require a well trained observer to detect the weaknesses. Forty-three patients, or 83 per cent, have excellent results, which means that there are no residua of the disease. In re-evaluating the percentages on the basis of those who lived, 47 of the 51 patients show very good or excellent results. This is 92.1 per cent.

PHYSIOLOGY

The concepts on which this method of treatment is based are elementary physiologic and orthopedic principles. These are:

1) A muscle which has lost its normal length (a short muscle) is a weak muscle. Deformities result because of short muscles.

2) Long continued spasticity or spasm will cause a muscle to become shortened.

3) Pain may be an etiological factor in muscle spasm. It is not the *principal causative agent of muscle spasm or spasticity*.

4) Sherrington's law of reciprocal innervation must be in effect for normal muscle action.

5) Normal circulation is necessary for the physiological return of muscle power.

It is thought that these concepts are best maintained by the use of curare, muscle stretching, active exercises, and activity from the onset of the disease or from as soon after the onset of the disease as possible.

No attempt will be made at this time to discuss the electrophysiology or electropathology of muscles affected by acute anterior poliomyelitis. All of these patients have been followed carefully and thoroughly with electromyographic studies. It is felt that this subject has no place in this presentation. A separate report of these studies will be made at another time. From the experiences with myography, it is apparent that certain of the published concepts will have to be reviewed carefully and, in all probability, be revised.

DIAGNOSIS AND DOSAGES

When a patient is admitted to the Monmouth Memorial Hospital at Long Branch, New Jersey, for observation as a possible acute anterior poliomyelitis patient, the procedure is as follows: A complete history and physical examination are done. An effort is made to determine the presence of muscle paralysis or paresis. Each joint is put through its range of motion to determine whether or not there is any loss of muscle length. A spinal tap is performed and, while the spinal fluid is being examined in the laboratory, myographic studies are made. If the diagnosis of acute anterior poliomyelitis is confirmed, the patient is given the first injection of curare while attached to the myograph machine; 0.9 unit of curare (Intocostin) per kilogram of body weight is administered intramuscularly every eight hours for the first twenty-four hours. After this period of time, the dosage is increased to 1.5 unit of Intocostin per kilogram of body weight every eight hours until all evidence of muscle spasm or spasticity has disappeared.

It must be emphasized that curare is NOT a "one shot remedy." From the nature of the disease, it should not be expected that one dose of this drug could possibly alleviate or obliterate permanently the hyperexcitability of muscle which is present. Therefore, it is necessary to administer the drug repeatedly until the disease has burned itself out and normal, or relatively normal, muscle and nerve physiology reestablished.

Much has been said, written and implied as to the dangers of curare. At the Monmouth Memorial Hospital, approximately 10,000 intramuscular injections of curare have been given to patients with acute anterior poliomyelitis. Its pharmacologic antidote, physostigmine, has been administered twice. It is doubtful that it was necessary either time. There have been no fatalities nor ill effects attributable either directly or indirectly to the drug.

PHYSICAL THERAPY

Physical therapy is instituted forty-five minutes after the first injection of curare. Each joint is put through a full range of motion or as nearly a full range of motion as possible at the time. This must be judicious stretching but pain is not the criterion of the amount of stretching necessary. The part is taken through its range of motion

until resistance is encountered. Then, with gradual pumping motions, that range of motion is increased as much as possible at that time. The amount of increase varies in each case, but it is a gradual increase, not an abrupt one which might result in torn muscle fibers, etc. *There never must be residual pain after stretching.* The stretching procedures are instituted three times after each daytime dosage of curare. The patients are taught to stretch themselves and one another. In addition to the stretching, active exercises are started immediately. Fundamental gymnastics of the Danish Group are utilized, stressing flexibility and coördination and getting strength coincidentally. It has been found that this approach to active exercises makes it more interesting for patients of all age groups. All activities are encouraged in order to keep the patients moving and busy. Occupational therapy, sports, tumbling, etc., form a part of the routine. Bed rest is discouraged except for febrile patients whose fevers are 102° or over. Mechanotherapy, hydrotherapy and electrotherapy are incorporated in the treatment.

FOLLOW-UP CARE

The follow-up care of these patients after discharge from the hospital is of the utmost importance. Each patient is required to report back for physical therapy daily. These patients are examined by a member of the staff at least once a week. The number of treatments per week is decreased as rapidly as the patient's condition allows. Any time that the attending orthopedists find evidences of retrogression, i.e., return of spasm as evidenced by loss of muscle length or muscle strength, curare is administered again as an aid to the reestablishment of normal muscle physiology. The physical therapy procedures, of course, have been continuous. All patients are examined at monthly follow-up clinics for at least the first year, when this is possible. It has not been possible to follow five of the patients. One, due to the fact that the family doctor frightened the mother about the after-effects of curare. One, because the grandparents insisted on prescribing the therapy. Two patients moved to Florida. The fifth patient was transferred to another institution. Her wedding announcement was received within eight months of this transfer.

Seventy-two patients, treated in 1945 and 1946, have been followed from the time of the onset of the disease to the present time with the following results:

- 1) No deformities have developed.
- 2) No braces have been used with the exception of a tongue spring for drop foot.
- 3) No crutches are being used.
- 4) Two patients use a cane occasionally.

PSYCHOTHERAPY

Psychotherapy is a most important part of this program. Every effort is made to make the patients feel at home in the hospital. Their own clothes are brought to them as soon as the isolation period is over. Favorite playthings, hobbies, etc., are brought to them from their homes. Toys, games and books are supplied. There is a combination radio-victrola for their use. The hallway becomes a parking lot for tricycles. For the children, meals are served on a long picnic table with benches. Birthdays always are celebrated with parties. The atmosphere never is allowed to be that of a sick room. The confidence and coöperation of the patient must be obtained by the physical therapists, the occupational therapists, and the nurses. Certain standards of behavior in treating patients with acute anterior poliomyelitis have been established. These are, in brief, as follows:

- 1) Never lie to a patient. If the patient is going to be hurt, tell him so.
- 2) Never bribe a patient in an endeavor to get his coöperation.
- 3) Make it a practice to spend some time in recreation with the patients daily. This may consist of roughhouse, reading, or innumerable methods of having the patients do things under the guise of play. This is essential so that the nurses and therapists do not become ogres, but maintain normal personal relationships with the patients. This is just as important for the adults as for the children. It is a real program based on elementary psychological principles.

CONCLUSIONS

1) It is believed that the described method of treatment of patients with acute anterior poliomyelitis will accomplish the following: (a) Shorten the period of hospitalization. (b) Decrease the number of personnel necessary to care for the patients. (c) Give better functional results. (d) Prevent deformities.

2) No claim is made that this is a cure for acute anterior poliomyelitis, but it is asserted that it is a better method of treatment.

<i>Nos.</i>	<i>Adm. #</i>	<i>Initial</i>	<i>Age</i>	<i>Pre-hosp.</i>	<i>Presenting Symptoms</i>	<i>Muscle Tightness</i>	<i>Muscles Involved</i>	<i>Type</i>	<i>Myo</i>	<i>Doses of Curare</i>	<i>Hosp. Days</i>	<i>Present Condition</i>
1	80151	DA	16 mos.	5 days	Temp., restless unable to walk, labored breathing.	Neck.	Intercostals, gluteals, hamstrings, quadriceps, tibials and triceps, surae peroneals and abdominals.	B	V	311	112	VG
2	82695	CSA	11 yrs.	4 days	Temp, headache, pain in back and r. arm, vomiting.	Back, neck, quads, strings	Right triceps.	S	V	142	54	E
3	81097	NB	2½ yrs	7 days	Temp, stiff neck headache, nausea	Opisthotonos, hamstrings, tibials	limping l. leg. All leg muscles weak.	S	V	36	19	E
4	81677	RB	6 yrs	15 days	Limping, seen in clinic.	Neck, back, hamstrings	Neck flexors, l. deltoid, hamstrings and quads, r. leg.	S	V	67	39	E
5	82920	PB	18 mos.	4 days	Slight ataxia, r. leg limp	Hamstrings, back.	R. tibialis, neck, flexors,	S	V	118	51	E
6	83735	RC	4 yrs.	2 days	L. leg limp (ref. from Fit-kin).	Hamstrings, and back.	L. quads and hams, neck flexors.	S	V	216	85	E
7	83450	JC	7 yrs.	5 days & 5 on medical.	Unable to swallow.	R shoulder, hamstrings, neck and back.	Tibialis, hamstrings, neck flexors, r. deltoid & triceps	BS	V	111	58	E
8	80747	AC	9 yrs.	3 days	Cold, nausea, pain in neck & back, unable to stand or walk.	Hamstrings, back, neck.	Hamstrings, r. leg muscles, gluteals.	S	V	65	34	E
9	86169	DC	2 yrs.	3 days	Temp, sore throat, r. hip limp.	R hamstrings & gastrocnemius	Abdominals, neck flexors, r. hip flexors.	S	V	26	24	E
10	82474	HC	2 yrs	2 days	Cold, unable to walk	Hamstrings & back.	L. quads & hams.	S	V	57	27	E
11	80620	SD	3 yrs.	4 days	Chills, fever, unable to sit up unable to use r. arm.	Neck, hamstrings, back, r. arm.	Flail r. arm, abdominals.	S	V	500	193	G
12	80506	DF	6 yrs	Ped 2 days	Cyanosis, twitching, temp. 103-105.	L. lower ext.	Intercostals, r. facial.	BE S	V	3	2	D
13	82241	CF	3 yrs.	3 wks.	Temp., nausea, unable to walk or stand.	Hamstrings, gastrocnemius, back.	Flail r. leg.	S	V	151	80	VG

<i>Nos.</i>	<i>Adm. #</i>	<i>Initial</i>	<i>Age</i>	<i>Pre-hosp.</i>	<i>Presenting Symptoms</i>	<i>Muscle Tightness</i>	<i>Muscles Involved</i>	<i>Type</i>	<i>Myo</i>	<i>Doses of Curare</i>	<i>Hosp. Days</i>	<i>Present Condition</i>
14	80918	KF	9 yrs.	10 days	Pain in thighs & limp, temperature.	Neck, left hamstrings, back.	Adductors l. and r., l. quadriceps and hamstrings.	S	✓	90	37	E
15	81398	BG	6 yrs.	2 days	Headaches, temp., pain in neck, flail r. arm.	Hamstrings, back and neck flexors, r. arm.	R. arm—flail, r. tibial, gastroc., abdominals, quad.	S	✓	225	109	VG
16	82319	JG	3 yrs.	3 days	Respiratory difficulty, unable to talk or swallow. Temp. 104.	Slight nuchal rigidity.	None.	B	No	2	1	D
17	83971	JG	2 yrs.	2 wks.	Cold, diarrhea, paresis l. leg, limps.	General.	L. hip & leg muscles all weak.	S	✓	47	21	E
18	81220	LG	12 yrs.	5 days	Respiratory and swallowing difficulties, comatose.	General.	L. facial, intercostals and abdominals.	BE	✓	106	41	E
19	82539	MG	18 yrs.	3 mos.	Fever, nausea, vomiting, paralysis l. arm.	General.	Deltoid (1) = 0.	S	✓	84	36	E
20	81996	HH	16 yrs.	2 days	Paralysis lower exts.	General.	Complete paralysis.	AP	✓	3	1	D
21	81304	EH	10 yrs.	8 days	Temp., swallowing difficulties, paralysis l. arm, stiff neck, nausea.	Hamstrings, neck and back, l. arm.	Flail l. arm, swallow muscles, abdominals.	BS	✓	157	63	E
22	81305	HH	9 yrs.	4 days	Resp. difficulty swallowing difficulty.	Back, neck, hamstrings.	Abdominals, tibials, l. biceps & triceps.	BS	✓	145	63	E
23	79490	LH	15 yrs.	16 days	Sore throat Weak arm (R)	Hamstrings Sacrospinalis.	R. upper ext. 3+	BS	✓	50	33	E
24	84451	MJ	22 yrs.	3 days	Cold, sore throat, stiffness, unable to walk.	None.	None.	S	✓	76	34	E
25	84726	FJ	3 yrs.	2 wks.	Ataxia, unable to stand or walk.	Hamstrings, back and neck, heel cords.	R. leg muscles.	S	✓	107	37	E
26	81291	AK	10 yrs.	6 days	Stiff neck, nausea, pain in legs. Unable to stand or sit. Headache, diarrhea, cramps.	General.	Flail r. arm and leg. Weak l. arm & leg. Abdominal leg flexors.	S	✓	410	144	VG

<i>No.</i>	<i>Adm. #</i>	<i>Initial</i>	<i>Age</i>	<i>Pre hosp.</i>	<i>Present in / Symptoms</i>	<i>Muscle Tightness</i>	<i>Muscles Involved</i>	<i>Type</i>	<i>Myo</i>	<i>Doses of Curare</i>	<i>Hosp. Days</i>	<i>Present Condition</i>
27	81139	GL	5 yrs.	2 days	Pain in l knee and thigh.	Neck & back quadriceps. L hamstrings	Abdominals L iliopsoas. L quadriceps	S	V	50	19	E
28	83893	RL	7 yrs.	4 days	Pain in left ear Cold, unable to walk on l leg	Back and hamstrings.	Abdominals and quads	S	V	47	32	E
29	82616	WL	10 yrs	2 days	Nausea, pain in neck, back and legs.	Hamstrings, sacrospinalis	Abdominals	S	V	65	27	E
30		HM	7 yrs	1 day	Pain in abd about umbilicus	Opisthotonos	Neck flexors. Abdominals		V			
31	81761	JM	8 yrs	11 days	Sore throat, stiff neck flail R arm	Back, hamstrings, wrist & finger flexors	Flail arm (R)	S	V	189	68	G
32	81173	RMcG	13 yrs	3 days	Nausea, sore throat, headache, stiff neck and back	Opisthotonos in general	L iliopsoas and hamstrings, triceps	S	V	140	51	E
33	81377	AM	35 yrs	3 days	Vomiting, cold, headache, pain in knee, paralysis l arm & leg, weakness r arm & leg	General	L arm and leg, abdominal, weakness r arm and leg	S	V	135	50	E
34	83460	JM	6 yrs	2 days	Pain in legs, limps on r	Hamstrings, back & back	R quads & hip abductors	S	V	54	34	E
35	83730	F.I	3 yrs	3 days	Fever, sore throat, swallowing difficulty (convulsions for years)	Hamstrings, neck and back	None	BE	V	105	193	E
36		JN	5 yrs.	?	Pain in neck, fever	Nuchal rigidity paraspinal	None	S	No	None	3	E
37	86706	JP										
38	82318	PP	3½ yrs	2 days	Pain in neck and back.	Pectorals, hamstrings, back and neck	Abdominals and neck flexors	S	V	39	20	E
39	83231	SP	10 mos	4 days	Sore throat & stiff neck	Hamstrings, neck, back, tibials	Flail r leg	S	V	221	76	VG
40	81257	DP	27 yrs.	3 wks other hosp.	Unable to move. Breathing and swallowing difficulty	General	Quadriplegia, abdominals.	BS	V	517	249	F
41	82512	WR	5 yrs	3 days	Abdominal cramps, Temp, pain r leg Unable to walk	Neck, back, hamstrings, quadriceps	Abdominals, neck flexors, muscles of r leg	S	V	162	79	VG

Nos.	Adm. #	Initial	Age	Pre-hosp.	Presenting Symptoms	Muscle Tightness	Muscles Involved	Type	Myo	Doses of Curare	Hosp. Days	Present Condition
42	80183	RR	12 yrs.	4 days	Fever, malaise, vomiting, pain in back and both legs.	Neck and back, hamstrings, quadriceps.	Peroneals and toe flexors.	S	Y	138	50	E
43	83331	WT	26 yrs.	3 wks.	Headache, fever, unable to move, painful eyes.	Gastrocs, hamstrings, back and quadriceps.	Quads and tibials.	S	Y	70	35	E
44	86240	WV	2 yrs.	2 days	Fever, pain in legs & arms, r. hip limp.	None (?)	Abdominals, neck flexors, hip flexors.	S	Y	33	26	E
45	81015	JV	5½ yrs.	4 days	Fever, sore throat, pain in neck, stiff neck and back.	Neck, back, hamstrings.	Neck flexors, abdominals & serratus.	S	Y	48	23	E
46	81252	CW	5½ yrs.	8 days	Fever, sore throat, pain in neck, weakness.	Neck, back, gastrocs & hamstrings.	Neck flexors, abdominals.	S	Y	67	27	E
47	80607	WV	5 yrs.	4 days	Pain in legs, stiff neck, fever.	Neck and back, hamstrings & gastrocs.	Abdominals, neck flexors & tibials.	S	Y	138	54	E
48	*	SMcN	11 yrs.		Pain in back and leg. Walking with a limp.	Neck and back, hamstrings & quadriceps, gastroc. & tibial.	Back and right leg.	S	No	78	81	E
49	*	CMcN	13 yrs.		Pain in back.		Back muscles.	S	No			E
50	*	H	14 yrs.		Pain in leg, unable to walk.		Right leg.	S	No	42	18	E
51	*	IH	22 yrs.		Opisthotonos, pain in back, headache, pain in chest.	Neck & back, hamstrings, & pectorals.	Neck flexors and back muscles.	S	No	57	61	E
52	*	RS	4 yrs.		Pain in l. arm and unable to use it.	General.	Biceps, triceps & deltoid.	S	No	45	20	E

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



DECEMBER 1947

CHANGING MEDICAL CARE IN OUR
CHANGING NATIONAL LIFE *

EDWARDS A. PARK

Professor Emeritus of Pediatrics
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SINCE I am addressing the pediatric section of the Academy, my audience may expect me to dwell on the social problems related to the care of children. But the care of children is just a part of the medical care problem of the population in general and cannot be separated, although attempts were proposed in the Pepper Bill and in the minority report No. 1 of the New York Legislative Commission on Medical Care. Accordingly I shall treat the topic in its general aspects. But before beginning I must make an explanation. I shall speak as if the medical care problem pertained only to physicians, hospitals, medical schools and the people although I realize as much as anyone that it concerns also dentists, public health workers, nurses, social workers, laboratory workers and all others whose duties are concerned with the maintenance of health and the problems of disease. I include the *people* with all the emphasis I possess, because, the general policies under which public funds are expended must be developed fully in the interest of those who

* Read April 10, 1947 at the Centennial Meeting of the Section of Pediatrics of The New York Academy of Medicine.

are to be served, the consumers of the medical care. Although by universal admission the sole authority in all matters pertaining to the applied science and art of medicine is the physician, in the economic aspect of medical care and to a considerable extent in the administrative the consumers, i.e., the people themselves, have equal rights and are equally concerned with the physicians. How much medical care will cost, how paid for, in what form it will be offered and just how it will be carried out, these are matters vital to the people also. So, on every administrative board which decides or administers medical care plans at every level, federal, state, or local, the receivers of medical care, the people, must be adequately represented together with the professional groups, the givers. I say this because I think that many physicians, probably most, feel that they are the sole authorities, the only ones who really know what is best and that the people should meekly receive what they decide to give. They forget that physicians are a vested interest and are instruments, not ends and our own selfish hopes and wishes loom large, so as to blot out parts of the perspective or hide the view altogether and in consequence we unconsciously think first of how to safeguard our own comfort and profit rather than the best interests of the people whom we serve.

If I remember correctly, in the brief time when the present Duke of Windsor was King of England, he visited the slums of London to see with his own eyes the housing conditions and on that occasion made a profound remark which evoked great praise in the British press. The remark was: "Something must be done about it." I think we are all convinced that something must be done about the present state of medical care but what form that *something* should take and how that *something* should be put into effect have stirred up great conflicts of opinion.

Why is it so necessary to change the present system of medical care? The present system has developed spontaneously to fit the distribution of money, not the distribution of medical need, and as a result it does not meet the medical need and, no matter how it might be extended, could never meet the medical need in one thousand years, for the reason that it operates on an incorrect principle. Another reason is that its fee-for-service system of remuneration keeps it from taking on a preventive character because the person who pays a fee to his physician at each visit goes to him only when sick. Another reason is that the

science of medicine has developed with such strides that the requirements of medical care have changed and groups of minds must now collaborate, since single minds can no longer be masters of more than small parts of medical knowledge. Moreover, as in industry, laboratories *and machines of great complexity have become essential*. As the result of all this the family physician who was once so adequate can no longer by himself meet all necessary services. He and his patients must have available specialists, x-ray service, laboratories, etc. Finally, this transformation of medical care into something far more complex and beneficial has unfortunately so increased its cost that it has risen out of reach of the majority of people. Without presenting the evidence the present happy-go-lucky, haphazard system of medical care has become outmoded and out of joint and is hopelessly insufficient and inadequate to meet the health requirements of the nation. This is one side of the picture. The other is that the great advances in science and industry have made possible higher standards of living. Moreover, the methods of science have been employed as never before in economics and sociology with the result that the facts of living, including health, have been studied and are intimately known. The knowledge thus gained has brought to pass a greatly intensified social consciousness and feeling of social responsibility, in brief, to an intensification of democracy in the finest sense of the word, meaning thereby the general acceptance of the principle that individuals have equal rights to fair shares of the comforts and benefits of life. Finally, large groups of the population, in particular labor and farm groups, have awakened to the idea that a new kind of medicine has come into being; wanting it, we see them on all sides organizing in the attempt to secure it. As a boy, I once heard President McKinley say in a campaign speech that he kept his ear close to the ground so that he could hear the voice of the American people. In reality I suspect he kept it about five feet four inches from the ground so that he would not miss a word from Mark Hanna. But, however that may have been, the legislators have now sensed what the people want and that is the significance of President Roosevelt's inclusion in his "second Bill of Rights," "The right to adequate medical care and the opportunity to achieve and enjoy good health," and the *Wagner-Murray-Dingell Bills, the first introduced in 1943 and the ancillary Pepper Bill* and the more recent Taft-Smith-Ball-Donnell Bill, represent attempts to realize this objective practically. To my mind, President

Roosevelt's inclusion in his "second Bill of Rights," January 11, 1944, of the idea that each citizen had a right to the best medical care quite apart from his financial position is a landmark in the medical history of the country, for the concept is so just, altogether right and feasible, fills so burning a need and was given such prominence through iteration by the late President that there can be no going back. Every plan for medical care since the enunciation of this principle has perforce been aimed, on the surface at least, toward that magnificent goal.

The general objectives in a Utopian medical care program are easy to see but difficult to reach. There must be an adequate number of splendidly educated physicians. An educational system must be set up to keep the physicians of the nation abreast of medical progress. New hospitals and centers of different sizes and functional scope must be dotted over the country according to community needs, and they must be serviced by groups of specialists and must be equipped with laboratories and all the latest machinery of medicine. The study of disease and its prevention must be constantly fostered and extended. Finally, the physicians themselves must be well paid and their lives and work made attractive in order to bring into the profession, which is entrusted with the health of the nation, the best talent possessed. These objectives or principles are at the basis of all the medical care programs in the more socially minded countries and the programs differ chiefly only in the degree of centralization and rigidity with which they are organized. I shall speak of some of these principles presently.

In this country there are great obstacles in the way of realizing the objectives just mentioned. The physical part of the program, that is, the construction of hospitals and centers, is the easiest part. It will not be difficult for the medical schools, if given facilities and prodded a little, to turn out more and better educated physicians. The experience in England and in New Zealand has shown that it is not so hard to give the population at large general practitioner service. The great obstacle—and it is enormously great—is psychological and lies in making physicians and the people, accustomed over years of habit to do something one way, to do it another. It would probably not be so difficult to change the habits of society; the great difficulty is in changing the habits and points of view of the medical profession, that is, to uproot and change over a system of medical care which is the outgrowth of centuries.

Another difficulty of a very practical nature in effecting changes in medical care is that in the profession of medicine itself there is no leadership. I shall come back to this subject later.

In the main, there are two divisions of thought in planning a system of medical care which will suffice to meet the health needs of everyone; one is that a new complete system, covering all the medical care needs of the entire population from "the cradle to the grave" ought to be imposed all at once, and the other that it is wiser to proceed gradually. Those in favor of the more radical drastic course are the supporters of the Wagner-Murray-Dingell Bill, S.1606, 1945. I shall not discuss this bill but merely express the opinion that, if it were passed tomorrow, medical care would be thrown into unbelievable chaos, for the reason that we are not prepared for its sweeping changes. We lack the physicians, hospitals, organization and the appropriate psychological attitude of the profession necessary for success and I do not believe that the people of the country are psychologically prepared for the change. The enactment of the bill now would result in a debacle such as would have occurred if the invasion of Normandy had been attempted at the outset of the war without the necessary troops, training, transport or equipment. Starting from scratch today, it would take fifteen years to become completely ready to meet the requirements of the bill. The dangers and difficulties of imposing revolutionary programs of medical care on an unprepared and inadequate medical organization are illustrated by the experiences in New Zealand which I shall discuss later. Before leaving the Wagner-Murray-Dingell Bill, however, I wish to point out that the bill itself is open to serious criticism. For one thing, it is altogether too highly centralized and rigid. On the other hand, it has great merits: it represents a splendid attempt to work out a medical care program clearly and logically. Its completeness has made it a huge target. It is the product of a fine idealism and it has had a magnificent influence in that it has led both the people and physicians to think, and in the case of Organized Medicine, to fear and to stir a little, for it has been handwriting on the wall. Finally, I express the opinion that in the end the form which medical care will take in this country will not be so far removed from the one outlined in the Wagner-Murray-Dingell Bill, but, I hope, more decentralized and flexible. I say this because in the medically progressive countries of the world the systems of medical care either in operation or projected are of that same pattern and that

pattern seems to be the one toward which the development of medical care is moving the world over.

The second division of thought, holding that it is wiser for us to proceed slowly in the development of a medical care program, is supported by the great majority of physicians. The general thought underlying this view has just been admirably expressed by President A. E. Morgan of Antioch College (Antioch Notes, February 14, 1947): "Social change should combine planning and improvising. We can tentatively plan limited phases of our common life, then watching the effects and taking into account factors first overlooked, we can replan and revise. By this step-by-step process, more than by a grand sweep of theoretical planning, will come a new society." I too hold this view but I am fully aware of the dangers inherent in the policy of trusting to a step-by-step process and I have no sympathy with the attitude of many of my medical friends who believe in doing nothing and trusting to "evolution," meaning thereby really doing nothing themselves to guide change but leaving the guiding to other people—lay groups, theorists and politicians. Evolution means change through the dying out of the unworkable and the survival of the workable. Evolution in this sense goes on all the time, no matter what we do, and determines or undoes in the end the work of mice and men. But it is a very slow merciless wasteful process and now there is no time to delay, for the public will take matters in their own hands through the agency of the government as they have done in England and New Zealand. Witness California at the moment!

But there are excellent reasons for going slowly, if we can only use them! Would it not be foolish to pass such a bill as the Wagner-Murray-Dingell Bill without waiting to see how the National Health Service Bill works out in Great Britain in the first year or two? Then we have before us the examples of Canada and New Zealand, the former setting a splendid precedent and the latter showing something to avoid. I shall refer to these again later. Then there are the Swedish and Russian systems which I should like to discuss now.

The Swedish system of medical care is a combination of State and private practice systems. There is a voluntary insurance system which by 1944 had spread to 42 per cent of the population, but a large number of those who were worst off financially were still not members. Because the voluntary system has not reached the lowest income groups and

because it has been so successful in the case of the others, the government is about to make the insurance system compulsory. The medical students are of the elite of the preparatory schools and the general medical education and preparation for practical work equal the topmost level of medical education anywhere in the United States. Hospitals and centers are distributed so as to be available to all and, also, complete medical services, i.e., including those of the specialists. I now quote from a letter from Professor A. Lichtenstein (*Journal of Pediatrics*, 28: 503, 1946):

"As can be seen from this account, we have in Sweden a combined system of state and private medical care. The state and the municipality, partly with the help of the sick relief funds, ensures that every sick person, irrespective of his financial situation, has the opportunity of obtaining the best possible medical care either in the hospital or outside. To this end, the best specialists in the country in various fields are available as salaried medical officers at hospital and as doctors for outpatients. The patient has, to a great extent, a free choice of physician. In my opinion, the free choice of a physician is necessary, for the patient, and for the physician, even in the case of members of sick relief funds, which embrace the largest portion of the country's population. The medical profession in Sweden is free, so that the individual doctor can, within a wide boundary, of his own free will choose the place and type of his activities. Even doctors appointed by the State or the municipalities are entitled, in so far as their work at the hospital permits, to carry on their profession with complete freedom.

"This system has, in my experience, functioned well, and on the whole fulfills the wishes of both the patient and the doctor. It is my opinion that a substantial state subsidy and control is necessary, if the health and care of the sick in a country are to function effectively and satisfactorily. The fears expressed by some doctors, that a state activity as regards medical care would hamper or prevent the practicing doctor's exercise of his profession, have proved themselves to be unjustified. On the contrary, the work, for example, of the child welfare centers has increased the interest of the public in child welfare and the care of sick children, and private pediatricians are sought in an ever-increasing degree. Such a development, however, presupposes that the state medical activities are not so organized as to make private medical practice impossible. I fear that should medical activities be entirely controlled by

the state, this would, in all certainty, lead to an unfortunate medical bureaucracy and also to an elimination of the personal contact between the patient and the doctor, which is a necessary condition for all good medical activity. Such a socialization would mean, for the medical profession, a lowering of the standard which is, however, to organize medical care in such a manner that every person, irrespective of his income, can procure the best preventive and curative medical care.

"In my opinion, the Swedish system shows very clearly that this can be done without undermining private medical practice."

Sweden has only 6,500,000 inhabitants (1945) and a geographical area smaller than France, and its population is homogeneous, disciplined and organized. The problem there was simple as compared to ours. Their system is the result of an indigenous growth and cannot be copied, but it demonstrates that it is untrue and therefore sheer nonsense to think that State Medicine and private practice systems cannot get on together successfully and happily or that State Medicine need interfere with the free choice of physician or patient or with the physician-patient relationship. Moreover it shows that through State planning and intervention medical service can be made available to all the lower income groups, not just general practitioner but comprehensive medical care. Finally, the system is approved by the physicians themselves. Professor Wallgren (Wallgren, A. *Journ. of Ped.* 30: 361, 1947) indeed, states that in general the physicians choose State positions in preference to private practice because of their greater security. I ought to add that in the development of the medical care plan in Sweden Organized Medicine has played a great part and with its almost dictatorial power is instrumental and perhaps the main force in keeping the State System at its high efficiency. I believe that if our medical care system equalled Sweden's we would have no medical care problem.

The trouble with evaluating the Russian system is that, though we know it on paper, we do not know it in operation. But on paper there are excellent features:—One is that there is a highly developed screening process in the education system designed to insure that the physician class have exceptional ability and there is further screening in order to separate out the ablest for the superior medical positions. Another is that the state makes special provision for the continued education of the practicing physicians throughout their active lives. A third is that the State pays the expenses of the medical student during the

years of preparation, so that medical education is open at all economic levels. So far as pregnant women and children are concerned, the health program is perhaps the most inclusive to be found anywhere. Of course the system is rigid and centralized, but the test is what it does for the health of the people and that I do not know.

If we accuse Russia of imposing an iron curtain, we cover our eyes when we look toward Russia with the blinding veil of prejudice. I suspect there is much to be learned from the medical care system of Russia and it is stupid to assume that it offers nothing to us just because we do not like the cut of its ideology. We must beware that in 20 years time we are not far outdistanced by that young, new thinking nation when measured in terms of what a medical system does for the health and security of the people. Dr. Mudd's report, in *Science* (*Science* 105: 269, 306, 1947) reveals the biological laboratories of Russia teeming with activities and ideas.

Then we have our own experiments in medical care, those in progress in Maryland, North Carolina, Washington, D. C., New York City, as well as many others scattered over all parts of the country, some started by physicians and some by lay groups. The hope and probability is that one or two of these experiments will emerge as unusually successful and serve as models. Unfortunately, I have not time to discuss these, but their spontaneous birth in so many places in so short a time is a portentous, healthful, promising sign.

A most important step, by general agreement wholly in the right direction, is the Hospital Survey and Construction Act (I shall refer to it as Hill-Burton Act) which is intended to furnish the physical setup for the extension of medical care to the areas of the country where most required. Its general features are excellent. The State survey is essential. The provision that the State can make its own plans based on its survey is admirable, and the limitation of the Federal role essentially to standards and guidance is as it should be. Under it the states have the desirable autonomy and yet the federal government has enough power to make certain of a carefully integrated and coördinate state and national plan. In brief, the balance between state control and federal control seems just and right. Then also it is a happy arrangement that the United States Public Health Service has the administrative assignment, for that splendid agency possesses uniquely the knowledge, organization and high ethical standards required for this particular purpose. I know

from experience that the United States Public Health Service can be of the greatest help in furnishing hospital plans. Finally, the establishment of the hospitals and centers is an absolute requirement if the very latest developments in Medicine are to be made available to all the people in the country.

But the Hill-Burton Act has some rather glaring deficiencies. It has no provision for federal funds to aid in the maintenance of the hospitals once they are constructed, and it has the same matching requirement for the poor and the rich states. This last means that the areas of the greatest need, the more rural states and communities and those with less wealth which should profit the most, are in actuality discriminated against. While the federal funds are allotted to the states in such manner that the poorer states may receive larger proportions of the amounts available, the result of requirement for uniform matching is that the poorer states are less able to take advantage of the federal offers. Thus no real equalization has occurred.

Bill S 545, introduced by Senators Taft, Smith, Ball and Donnell, I shall refer to as the Taft Bill. It is at the opposite extreme from the Wagner-Murray-Dingell Bill and is obviously written to appeal particularly to those to whom Federal control is anathema. The Taft Bill vests essentially all the authority in the individual states and reduces the Federal control near to impotence. If the Wagner-Murray-Dingell Bill was carefully thought through and made to face issues squarely, the Taft Bill is poorly thought out and avoids controversial issues, except for its central thesis of states' rights, by passing them on to be fought out in the individual states. It contains provisions fraught with peril. For example, the Bill provides that "no plan or modification shall be disapproved because the (Federal) Director disapproves of the methods proposed." This would probably be interpreted as prohibiting the establishment of Federal standards which a state would have to meet in order to have its program approved. Virtually all of the existing health legislation requires the establishment and maintenance of personnel standards on a merit basis. Such Federal legislation has been a most important factor in taking politics out of Health Department appointments. Such a merit system clause was in the original Taft Bill introduced last year, but its omission is conspicuous in the present bill. The removal of this would open the State programs to political appointments. Proposals in the bill would allow the State to purchase services through any non-

profit voluntary insurance program without any standards whatsoever. This would permit state and federal funds to be used to subsidize poorly operated voluntary insurance programs. Moreover, within the National Health Agency seven units are established, one of which is the new Office of Medical and Hospital Care Services. This unit is administratively entirely separate from the United States Public Health Service and the Children's Bureau, i.e., the existing federal health agencies have been completely by-passed. This arrangement creates obstacles in the way of integrating preventive health services and curative health services. If the bill were passed as it stands, there could be as many different systems of medical care as there are states. Some of these in the more progressive states would probably be very good, in some other states exceedingly poor and all would be laid open to the possibility of political intrigue and inefficiency. If the passage of the Wagner-Murray-Dingell Bill would produce chaos in medical care, the Taft Bill would produce national confusion and perhaps corruption and would establish an inefficiency from which it might be impossible to recover. It would span the way to the perpetuation and extension of the poor features of the present system of medical care without the assurance of new good features. The bill has other questionable provisions, one of which having to do with a proposed extension of voluntary insurance to the medically indigent groups, I discuss later. But the bill is an example of careless thinking, or not thinking at all, and the fact that such a manifestly inferior measure could be proposed by our legislators is depressing to those who perceive how glorious a medical care program might be.

If it is wrong to give all the power in health legislation to the Federal Government, it is worse to place it all in the states and to have no national integration or coördination. In determining Federal and State relationships there must be a happy medium, in which the Federal Government establishes the general scheme and fixes minimum standards and the states have freedom to develop their own systems within the Federal structure. The plan for compulsory health insurance which the Canadian Medical Association has recommended to the Canadian Government is in such marked contrast to the Taft Bill in the wisdom with which the Federal-Provincial relationship is arranged. Their recommendation (*The Medical Profession and health insurance*. A submission to the Special Committee on Social Security of the House of Commons

by the Canadian Medical Association 1943) reads: "If Provincial autonomy is to be maintained as suggested above, it is extremely important that a sufficient degree of federal control be retained. This control should be limited to such matters as the extent and the standards of the services, as indicated previously. It is important, however, that control be maintained as it is only through this means that a satisfactory degree of uniformity can be obtained. Unless there is considerable similarity in methods and program in matters of disease prevention and control, the results from the national viewpoint will be jeopardized.

"On this basis it is recommended that the federal administration be under the Minister of National Health, with an advisory Dominion Council on Health Insurance. . . .

"In the provinces it is strongly recommended that the plan come under a NON-POLITICAL INDEPENDENT COMMISSION which might be responsible to the legislature through the Provincial Minister of Health. . . .

"Among the details left to the Provinces might be the income level below which the residents would be included under an obligatory plan of insurance, the rate and method of payment for all services, professional and institutional, the best means of obtaining full preventive and public health services within the provinces and the particular means which might be necessary to safeguard adequate teaching in the medical schools and teaching hospitals." (J. Pediat. 3:228, 1947)

The Taft Bill contains a suggestion that voluntary insurance be extended to the medically indigent through the use of tax money to pay the cost of coverage in voluntary prepayment plans. This raises the topic of insurance under public auspices, supplemented, as necessary, from general tax revenues. It is probably the best method for financing complete coverage for medical care for the entire population of the nation. Its merits, as an immediate measure, will be discussed by Dr. Ernst Boas in the April number of the Journal of Pediatrics. As just stated, the Canadian Medical Association recommended in 1943 to the Canadian Government a compulsory health insurance system which could be made to include everybody or only those in certain income levels according to the determination of each province. I do not believe that we in this country are yet prepared for universal health insurance, either psychologically or materially. The enactment of universal health insurance, without an intervening period of planning, would throw the full weight of providing necessary care for the entire

nation upon our present limited resources before they have been built up to the required strength. If, however, a Federal-State health insurance scheme supplemented, when necessary, from general taxes were made available to the low and middle income groups, the burden on the physicians and medical care resources of the country would still be great, but, perhaps, not too great, if time were granted for planned gradual adjustment.

Voluntary insurance has been taken up by the public like wild fire. The Blue Cross has now 24,250,000 subscribers, one-fifth of the population of the country, and prepayment medical care schemes such as those offered by medical and consumer groups have been extended considerably. But practically all voluntary insurance plans supply only partial medical care and that for only a limited period of time in the sense that they cover only catastrophic illness and they do not provide for preventive medical care. These deficiencies are tremendous and keep the present plans far from meeting the total need of even those financially able to subscribe to them. Moreover, the plans are circumscribed by specific factors, such as occupation, economic status, residence, race, etc. Nevertheless, the voluntary hospital insurance plans have been a great benefit and their popularity indicates that the prepayment principle is generally desired. My medical friends, and they are many who favor a hands-off waiting policy in regard to the development of medical care, advocate voluntary insurance spread until it reaches everyone who needs it. But it is obvious that voluntary insurance can never spread to those who need it most, namely, to the low income groups, for they can never afford it. Furthermore, experience shows that plans offering complete medical coverage are necessarily too costly for most families, even those in the middle income groups. This accounts for the slow growth of voluntary medical service plans.

Returning now to the Taft Bill, it suggests undertaking to provide care for medically indigent persons through payment of insurance premiums with tax monies to all types of non-profit voluntary plans. This would appear to be a policy based on fallacious reasoning since it would involve inappropriate use of public money and would be unsound governmental procedure. It is a long-established principle that tax monies should be expended by public agencies which are accountable to public officials representing the tax payers. This is a basic principle in the organization of our government and hence a vital consider-

ation against the Taft Bill proposal aside from the fact, as I have pointed out above, that voluntary plans do not generally assume responsibility for meeting more than the very partial medical needs of their members. It seems astonishing that Senator Taft and his associates should have allowed to be introduced into his bill a suggestion flaunting this time honored principle.

In any prepaid medical care program in which the care offered is to cover all requirements the method of compensation of physicians is of great importance, and since our present medical care system is founded on a sliding fee-for-service remuneration, I shall briefly discuss the fee-for-service method of reimbursement and give the experiences with it reported from New Zealand. The fee-for-service method of payment of physicians has the great merit of stimulating competition, and this is its virtue. However, it has serious drawbacks: Most important it stands in the way of preventive medical care, for the obvious reason, as previously mentioned, that, if a person has to pay a physician for his visit, he will not go to him until sick. The method interferes more than anything else with the naturalness of the patient-physician relationship. It is not democratic, for it creates economic and social distinctions. High priced physicians in the main have rich patients and low priced physicians the poor and the low priced physicians in consequence are the ones who carry the great burden of charity and are not so well equipped to do first quality work in consequence of heavier load and poorer facilities. Moreover, the method of payment stimulates avariciousness and breeds fee splitting. In short, it is the chief cause of criticism or of actual charges against the medical profession. Finally, as previously pointed out, it gives a wholly wrong distribution of medical care. When it is introduced into a prepaid complete coverage medical care plan or one based on direct payment by the State for service rendered, it is difficult to control and is likely to wreck the system. The New Zealand experiment in medical care illustrates the difficulties caused by the fee-for-service variety of payment.

The New Zealand plan in brief is that the government provides medical care for everyone by paying for medical and pharmaceutical benefits according to fixed rates. The fee-for-service or "direct claim" system was intended by the government to be the standard and has been the one chiefly used, though capitation and salary reimbursement have been employed to some extent. Under the fee-for-service system the

patient signs a form stating that service has been rendered and the physician sends in the form to the health department and receives 7s 6d per service. This is the ordinary arrangement but many physicians have used a so-called "Refund System" or "Token System" which makes the patient add 3s from his own pocket, so that the physician nets 10s 6d per service. I shall not discuss the arrangements for specialist or laboratory services, but with this brief explanation will quote from my informant, a prominent physician in New Zealand, whose name I shall not give because in a communication just received I do not have his permission: "Under these schemes the doctors have become extraordinarily prosperous. It is comparatively easy to work up a good income almost anywhere except perhaps in rural districts where a lot of travelling is still necessary. Actual figures of doctors' incomes are not published, but some which are almost fantastic are commonly mentioned in parliament. The highest rewards are obtainable under a company arrangement, where the principal can pay handsome salaries to juniors and still reap rich rewards. The individual man can make a big income by dint of hard work and organization. . . . From the doctor's point of view perhaps it is a good thing that by ordinary work he can secure very adequate rewards. . . . The emphasis is placed on the number of acts done rather than on quality. Indeed we find the doctor personally doing a number of trifling things in his practice that ought to be done by a nurse or secretary, but are not so done because it is worth 7s 6d a time to the doctor, if he does them. . . . The poor man's cough is now as profitable as the rich man's and certain areas both urban and rural, formerly poorly served, have now medical men on the spot. So far so good, but a further effect is to concentrate medical men in the cities as against country districts where travelling is greater. . . . Moreover, as between general practice and specialists, scientific and teaching work there is a disproportionate attraction to the former. The pathologists, radiologists, hygienists and teachers in the profession are almost all maintained by salary and are the Cinderellas in the financial sense. . . . The quality of service suffers under the fee-per-service structure with its emphasis on quantity rather than quality. The tendency is toward quick superficial work and the avoidance of difficult subjects, times and places."

According to the New Zealand system the patient pays nothing for pharmaceutical benefits—merely hands in his prescription and counter-

signs it when he receives his bottle. The total cost of pharmaceutical benefits has risen steadily and now reaches almost fantastic proportions. For the fiscal year 1945-1946, the cost to the government for payment to physicians was 1,633,514 pounds and the cost to the government for pharmaceutical benefits was 1,133,366 pounds, a figure only one-third less. The enormous proportions of the expenditure for pharmaceutical benefits reveals what must have happened, namely, the doctor reverted to the old method of satisfying the patient in the quickest way by giving a prescription. I believe it will be difficult now for New Zealand to extricate herself from the poor system on which the general practitioners have grown fat.

The New Zealand experiment teaches lessons: First, the medical care program was thrust on the country by the Labor Government without adequate consultation with medical groups. A chief reason for this was that Organized Medicine there was not conciliatory to change in medical care, like the British Medical Association in the Lloyd George regime and Organized Medicine in this country now. Thus, the medical care program was poorly thought out and designed. Second, it was commenced before the organization for medical care the country over was able to cope with it; i.e., it sought solution by removal of economic barriers alone. Third, the rank and file of general practitioners profited, as is bound to be the case in any medical care system in which the medically indigent become medically solvent and as they will do in this country as soon as the medically indigent group ceases to exist as such. It is astonishing that practicing physicians in this country do not see that their incomes will be increased the moment the medically indigent group becomes a secure source of revenue. But before leaving the account of the New Zealand experience with the fee-for-service method of reimbursement I ought to caution against the impression that the medical care program there has been a failure. Whatever its defects in administration, it has made general practitioner service available to all and must have given feelings of security difficult to evaluate to low income groups particularly by removing the specter of pauperizing illness. The total success or failure of a medical care program can be measured in just one way, its results on the happiness and health of the people.

It is obvious that a *sliding fee-for-service* method of payment—I refer to our present system in which the physician has the right to

charge what he thinks he can get—would vitiate and hence be unworkable in any prepayment scheme which undertakes to furnish complete coverage medical care. But a regulated fee-for-service system has been used in Sweden successfully. However, I personally doubt if even the *regulated fee-for-service* method can be used successfully in any large prepayment program *including all medical services* in the complex conditions of this country because it is so easily abused and difficult to control.

I shall not discuss other systems of payment to physicians in nationwide health plans except to say that in New Zealand and in England physicians on the capitation method of payment have liked it and capitation has some advantages, particularly in promoting preventive medical care. It is planned to try it in Baltimore for the care of the indigent as part of a plan which is highly original and has great potentiality. I wish I had time to describe it. Probably in any nation-wide medical care system all three methods of remuneration—controlled fee-for-service, capitation and salary—ought to have their places.

I now come to a subject which seems to me of great importance, namely, the participation of the medical schools in medical care plans, but I have time only to touch on it here and there.

First, there must be more physicians to cope with the increased burden of medical care under any plan which includes full care of all the people. Dr. Parran has supplied some figures in this regard. The medical schools of the country now turn out about 5,200 graduates a year. Adding the 7,000 graduates accrued as the result of accelerated war education, there would be produced in the next 20 years, i.e., by 1967, 111,000 physicians. During the same 20-year period, 77,000 would be lost from death or retirement. This gives an estimated net gain by 1967 of 34,000 physicians. But the gain in population by 1967 will require 27,000 additional physicians to maintain the existing ratio of physicians to population. This reduces the net gain in 1967 of 34,000 physicians to 7,000. But a whole variety of unrelated factors, such as specialization and the increased complexity of medicine, the spread of pre-payment plans of medical care, the inclusion of the medically indigent, the supply of the newly created health centers and hospitals, etc. all unite to increase the requirement for physicians above the present physician-population ratio. To meet this, Dr. Parran calculates that by 1967 our medical schools must produce nearly 50 per cent more

graduates than at the present time, i.e., 7,800 instead of 5,200. It follows that either the capacity of our medical schools must be increased or else new ones must be created. There would be great opposition at Johns Hopkins to any large increase in the number of medical students because of a lack of expandable teaching facilities, and this attitude probably prevails in the other full-time medical schools. I personally hope very much that the increased demand for physicians will be met by the formation of new full-time medical schools which could then be placed in the areas of need just like the new hospitals and medical centers to be constructed under the Hill-Burton Act. But I might remind you that though new hospitals and centers can spring up in 2 years, from 7 to 10 years at the least would be required to furnish the 50 per cent additional quota of physicians, and this means that to attain Dr. Parran's 50 per cent increase in the number of physicians by 1967, it will be necessary for the medical schools to plan on turning out 100 per cent more graduates immediately, i. e., double their admissions at once.

Second, our medical students should be better selected. The health of our people is so important that physicians should be as fine and intelligent a class as we possess. The standards in medical education ought to be high and the inducements to a medical career made great.

Third, medical education should be extensively reorganized and improved in two parallel ways. First, it should be integrated much more closely with public health and the student taught to regard the prevention of disease to be as much his duty as the care of the sick. In the list of objectives which the Canadian Medical Association adopted for presentation to the Canadian Government the first on the list is "The Promotion of Health and the Prevention of Disease." Preventive medicine, or the proper attitude toward it, cannot be taught by placing in Medical Schools separate departments of Preventive Medicine. Why not establish separate departments of Therapeutics? Preventive Medicine is an every day, every hour, every minute part of clinical medicine and must be taught by clinical teachers themselves in connection with their cases and daily work and the teachers of clinical medicine themselves must learn the new philosophy. Then the teaching must be reorganized so as to give to the student a broad social viewpoint, so that he can join in a concerted effort to furnish medical help in all aspects to all people with intelligence and enthusiasm. Finally, practical training in hospitals or centers should be at least three years, making the

total period of preparation 7 years before risking a young doctor on the community.

Fourth, the private medical schools must have State aid. At Johns Hopkins the tuition is \$600.00 a year. The cost to the Medical School of the education of the student is \$3,900 per year. With the shrinking resources and the disappearance of the old private supports and without the addition of new, the full-time medical schools cannot continue.

Fifth, the State must aid the student financially because of the long costly preliminary years of preparation, if medicine is to attract the finest of our young men. During his 4 years in Johns Hopkins Medical School, the cost of the support of the medical student, apart from tuition, is from \$1,300 to \$1,500 a year. During his hospital training as intern, he receives no stipend. Only to those who command financial resources and can wait the years of preparation is a medical career open. If the State salaried the young doctor during his three years of hospital experience, a great part of the load would be lifted and after that was over it would be fair for the State to draft him on a salary basis for two to three years for some rural community where physicians were required. This idea is suggested in the proposals of the Canadian Medical Association to the Canadian Government. A somewhat similar plan has been introduced into the medical care scheme of North Carolina. The plan would be similar to that now in operation in our Naval and Military Academies.

Sixth, I now come to an idea of the greatest importance, namely, that the medical schools must agree to extend their teaching obligations to the practicing physicians. One of the worst features in our present system of medical care is that practicing physicians of the community have no means of keeping up with medical progress and in consequence are left in intellectual, quickly turning to spiritual, stagnation. Of course, many of the more progressive practicing physicians go to medical schools for refresher courses yearly or attend medical meetings, where practical surveys of various topics in medicine are given by experts. But the education of practicing physicians ought to be organized so as to be a regular part of their professional lives. Of course, medical schools could offer refresher courses but by general admission this method is not the best way to teach. The method which has tremendous possibilities is for the medical schools to extend their activities into the subsidiary or-satellite hospitals and centers created by the Hill-Burton

Act. I do not know quite how the plan could be best worked out, but I suggest that the Medical Schools send to the satellites on some rotation plan groups of their able, splendidly trained specialists in internal medicine, pediatrics, x-ray, pathology, biological chemistry, etc., with the understanding that these men act in them as heads of the general services in their respective fields, consultants and teachers. These emissary representatives of the medical school faculties would be full time on salaries and would not compete with local physicians. The salaries would have to be good ones. and furnished to the Medical Schools by the State, for the Medical Schools must be given complete freedom. I also suggest that the Medical Schools supply the satellite hospitals and centers with interns, who would work under their emissary preceptors from the Medical School just as at the home hospitals. By general agreement the finest medical care anywhere in this country is that furnished by the Medical School Hospitals and the suggestion made would give the remote communities that same splendid level of care. The teachers assigned to the satellites could give clinics and systematic instruction of various kinds to the practicing physicians, and, much more important, could go over their patient problems with them in the home, out-patient clinic, ward, operating room or laboratory. There is no teaching so good for teacher or student as case teaching. This extension of the Medical Schools to include the education of the practicing physicians would have the greatest influence I can conceive of in raising the morale, the standards of work and the enlightenment of the medical profession of the nation. I make one further suggestion, that if the private medical schools will not or cannot enter into this plan, the State subsidize the State supported Medical Schools and create where needed new full time State Schools of Medicine whose particular duty it will be to organize instruction for the practicing physicians which will keep them abreast of medical progress.

A participation of the Medical Schools in medical care is envisioned in the National Health Service Bill for England and Wales.

As intimated, the policy of gradual development of a medical care program has its perils, and the perils are that the moves forward will be in wrong directions or will lead into pits, like the thinly concealed ones in the Taft Bill, or remain isolated when they ought to be coördinated. Gradual development is the best policy provided it is carefully thought out, but is dangerous if not thought out at all. Take the Hill-

Burton Act for example. This was designed to make available the latest advantages of group medicine to the needed areas. Where will the specialists who are to form the groups come from? They will not spring from a ground sown with dragons' teeth like the robot warriors in the fairy tale. They can't be enticed to rural areas by the prospects of large fees. If the attraction must be good salaries, then a little planning could bring the wonderful uplifting influence of the medical schools into the program. Again, the construction of the hospitals and the centers makes at once an increased demand for physicians; yet, as pointed out, physicians, in particular specialists, are seven-year products at least, and yet no steps have even been contemplated to increase the output of the medical schools. Granted that it is impossible now to think through the problem of medical care to the very end, it is certainly possible to think a considerable way into it and some requirements are common to any comprehensive medical care plan, and are as evident now as 20 years away. There is no planning in what is going on now and this is because there is no medical leadership. The movements, such as voluntary insurance and the isolated experiments in medical care, were born in the minds of enterprising, socially-conscious groups of physicians or lay organizations working outside Organized Medicine. If Organized Medicine had been responsible for these isolated attempts, even if unable to formulate any complete program of its own, it would have much to its credit. Organized Medicine should have furnished the leadership, but not only has it not shown leadership, but has opposed important developments, which have gone on, none the less. But in spite of its dead weight Organized Medicine, resisting on occasions, has been dragged forward by the sheer power of outside opinion and the force of example elsewhere a long way since 1938, when it tried to block the formation of the Washington Group Health Association, until now it endorses the non-profit prepayment or voluntary insurance principle and recognizes the necessity under certain conditions of Federal Aid in medical care plans. But its much touted "Ten-point program" is no program in any original, dynamic or constructive sense, or, indeed in any sense, but only a series of pious platitudes and highly qualified endorsements of policies or activities, initiated in the first instance by isolated groups of liberal minded socially conscious physicians or laymen working independently of it. Its primary concern throughout as judged by its behavior has seemed to me to be aimed consistently at the preservation at

all costs of the medical care system as it exists today. Disturbed, it cries out in the words of Fafnir coiled around his treasure, when the youthful Siegfried, the personification of the new order, approaches with his magic sword, "Lass mich schlaffen."

In this critical period of change, when the handwriting appears on so many walls, the behavior of Organized Medicine is humiliating, and its leadership has seemed incredibly stupid and in such contrast to the up and coming progressive attitude of the Canadian Medical Association, which has boldly and unqualifiedly taken the leadership and presented to the Canadian government their own plan for a system designed to provide comprehensive medical care for everyone. When I asked a prominent Canadian physician how it happened that the Canadian Medical Association was so open- and liberal-minded, he replied:—"We saw what was coming and decided it would be better to develop our own program, one which we liked, rather than to have one forced on us." He remarked further, "We have some big leaders." I think that Dr. Fishbein has had an opportunity, such as comes to few, to lead Organized Medicine in our country in a program of medical care which would have been a monument to an enlightened and progressive spirit, but he chose the opposite course, the course popular and easy at the moment but not the one destined to appear creditable in history. Without leadership it is impossible to concert a plan, but I express the view that fresh legislation should be introduced into Congress along a middle ground between the proposals of the Wagner-Murray-Dingell Bill on the one side and the Taft Bill on the other, legislation which among other things would give the Federal government enough authority to develop and maintain the general structure and standards of a comprehensive medical care system but would allow the individual states freedom to develop their own programs within the general outline; which would preserve private practice, as it now exists, for the upper income groups but would make medical care available through a *government* insurance scheme to the lower income groups, not merely general practitioner service but the most intelligent broad reaching medical care which scientific progress and specialization through group practice have now made possible anywhere and which, finally, would augment and implement existing medical schools and establish new ones in needed areas, so that they could turn out annually the requisite number of excellent physicians and could assume regionally the continuous educa-

tion of the practicing physicians as a regular part of their duties preferably through extension into the newly created hospitals and centers.

A few weeks ago President Truman requested the Federal Bureau of Investigation to investigate all government employees in order to discover and eliminate Communists. I sometimes think that governments are more in need of psychiatrists than are individuals. The way to free this country from Communism is not, in my humble opinion, by Gestapo espionage and persecution, methods which history has shown over and over and over again merely drive ideologies underground and by repression and dispersion give them increased impetus, but to make our own people so much better fed, housed, clothed and educated and happier and freer than others that Communism will wither and die for lack of soil of misery and discontent to grow on. I can think of no better beginning than with the least possible delay to reorganize medical care so that in full measure and in most modern kind it would be available to each citizen with all its benefits.

THE ETIOLOGY OF BENIGN
PROSTATIC HYPERTROPHY *

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THROUGHOUT every one of the branches of medicine there runs an identical methodology in scientific development which is so similar that it must be considered as a basic pattern of human thought which man is conditioned to use as he investigates the unknown. The evolutionary stages are historically as well as in order of increasing importance, Speculation, Observation and Experimentation. In considering a subject it is well at times to reflect on which stage one finds himself and how important that phase may be with reference to the others.

Consideration of the etiology of disease entered medicine as a late and sophisticated development. Early man, no doubt attempted by preference to cure his pain and malaise through mystical means and when these therapeutic agents often proved to be erratic and capricious he reluctantly turned to more earthy methods. I presume that the first attempts at treatment were considerably later superceded by primitive diagnosis since some sort of a classification seemed to be helpful if not prerequisite to therapeutics. The classification of illness naturally led to thought about the causation of disease.

What is the etiology of benign prostatic hypertrophy? There was much early speculation about it and many theories have invoked such diverse factors as venereal disease of the several sorts, inflammation, arterio-sclerosis and various human sexual habits as well as celibacy. The causation of disease is not nearly so simple as it seems at first glance. In a few fields one can give succinct although sometimes superficial statements of etiology. For example, it is easy to state that a waxy bacillus is the cause of tuberculosis and that a green streptococcus is the inciting agent in sub-acute bacterial endocarditis but even here such

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things as resistance of the host complicate the problem in certain individuals and species.

The etiology of prostatic hypertrophy seems to be particularly difficult to investigate since many of the characteristics of the disease are peculiar to man. Since experiment thereby is greatly limited we are largely thrown back on observation so that concerning the cause of the enlarged prostate only an approximation can be given at this time. I wish now to consider how far contemporary morphologic and functional knowledge can provide a limiting frame in which the etiology should fall.

Benign prostatic hypertrophy so far as is known occurs only in man and dog and it has not yet been successfully induced in the laboratory. Probably any attempts at experimental production should involve the dog as the experimental animal; it is a fundamental dogma of the laboratory that any disease which occurs spontaneously can be experimentally reproduced but unnatural disease may be something else again. The disease differs in man and dog. Canine prostatic hyperplasia in essence is a cystic hyperplasia of epithelium. The cause of the cysts is not ductal obstruction since plugging the ducts with a graft of striated muscle¹ although producing cystic change does not result in hyperplasia. Also the injection of India ink into the dilated cysts of spontaneous cystic hyperplasia reveals that the ducts are patent. Always tall columnar epithelium is present but its functional capacity is damaged. The prostatic secretion in canine prostatic hyperplasia is identical with that of young adult normal dogs but the volume is greatly reduced. A fist sized canine prostatic hyperplasia (100 grams) secretes much smaller volumes (2-5 cc.) than does the 10 gram gland of a normal young adult (30-50 cc); but each prostate produces the same type of fluid.

Canine prostatic hyperplasia is under androgenic control. The disease does not occur in castrates. Testicular excision causes prompt atrophy² and differing from the hypertrophy of man, where the effect is slower, profound involution of the tumor occurs promptly after estrogen. Dogs feminized by estrogen produced by Sertoli cell tumors of the testis³ have been extensively investigated; they never have canine prostatic hyperplasia. The disease only occurs in old age. Nearly all ancient dogs (objective evidence—worn teeth and cataracts) with functioning testis² have this disturbance. Age itself does not confer on prostate gland the necessity for epithelial proliferation. We have injected androgen,

testosterone propionate, 10 mg. daily for 3 months, in 3 dogs known to be older than 16 years and castrate in early life; in each case a normal prostatic gland with no signs of cystic hyperplasia resulted.

We deduce from all this that androgen and senility are important factors in the hyperplasia of dogs and that the senility factor is not a matter of chronology alone. The time component is the expression of continued stimulation by androgen over long years. The evidence for cystic hyperplasia being a neoplasm is presumptive but not clear cut in the dog.

It is well now to consider the following facts and their interpretation concerning the prostatic hypertrophy of man.

1. *The lesion is composed of spheroidal neoplastic nodules.* It is not an hypertrophy at all; however smooth the lesion may appear in the gross, spheroidal masses are invariably found on dissection. The nodules are always multiple. At times the right and the left sides of the prostate are asymmetrically involved, a larger nodule being present in one portion than the other; however nodules are always found in each side of the gland and a single spheroid in the prostate must be a rarity.

The spheroids usually are composed of 3 elements, epithelium, smooth muscle and fibroblasts; less often epithelium may fail to be present. Strictly, multiplicity of nodules in pathology indicates only that there are multiple centers of origin of the lesion. Since pure myomas and fibromas occur in addition to the characteristic epithelial containing growth it may be deduced that the spheroidal nodules of the prostate are benign neoplasms. Further benign prostatic hypertrophy⁴ has an appreciable aerobic glycolysis (QLO_2 2.21) and possession of this metabolic pathway is one of the characteristics of tumors. The content of citric acid, aconitase⁵ and acid phosphatase in the prostatic adenoma is not impaired. In many respects the spheroidal disease of the prostate resembles fibroid tumors of the uterus except that epithelial proliferation is absent in the latter. Incompletely removed neoplasms usually regenerate and this explains the bad results of transurethral resection where it is impossible regularly or indeed frequently to remove all of the spheroids.

2. *Growth of the human prostate is not finite.* In his study of 733 human prostates Teem⁶ quaintly but accurately observed "The prostate reached the adult size in the third decade of life, and from then on the curve for the average weight gradually rose." Benign prostatic hypertro-

phy was observed in 5 instances by Teem between age 30 and 39 years. Moore^{7,8} did not encounter the disease before age 39. The disease increasingly affects the prostate with increasing age to the limits of life. In Moore's study 75-80 per cent of all men after 80 years of age had prostatic hypertrophy. The age influence is expressed in a homely way in the saw that "children have all of the urologic diseases of adults except pyelitis of pregnancy and benign prostatic hypertrophy."

3. *Only the medullary region of the prostate is involved by benign prostatic hypertrophy.* Tandler and Zuckerkandl⁹ first expressed the concept that the disease is essentially pre-spermatogenic in origin and involves the periurethral regions exclusively and that the posterior region of the prostate does not become the seat of hypertrophy. It was the opinion of these scholars that the original lesions arose as budding of sub-mucosal glands of the urethra. Reischauer¹⁰ and later Moore⁸ stated that the earliest lesion was a sub-mucous nodule of stromal cells which were devoid of elastic tissue. Reischauer believed that the fibro-myomatous tumor often became invaded by epithelium. These findings are not consonant with our observation that the spheroidal nodules may arise in any part of the prostatic medulla.

Although the prostatic glands arise as buds from the urogenital sinus, it has been clear that a duality of structure exists in the prostates of many species. In the guinea pig and rat¹¹ as well as the monkey¹² a specific region of the prostate exists which is able to induce coagulation of the seminal vesical secretion. Further in the rat and mouse^{13,14} this area—the anterior prostate or coagulating gland, responds differently to estrogen from the main body of the gland; the acinar epithelium becomes transformed to squamous cells in the anterior lobes while the dorsal and ventral lobes remain uninvolved.

In the dog the response to estrogen is clear cut in varying portions of the gland; only the posterior or dorsal segment of the gland responds to estrogen¹⁵ by forming squamous metaplasia. In the presence of injected estrogen and androgen the ventral portion of the canine prostate responds by forming tall columnar epithelium while the posterior region undergoes squamous transformation.

In his classic embryologic study of the human prostate Lowsley¹⁶ observed that the posterior lobe of the prostate arose as an independent structure originating from the floor of the urethra below the ejaculating ducts.

In man prostatic cancer usually arises in the cortical region of the prostate¹⁷ and the difference in the type of tumors arising in the medullary region seems to indicate a fundamental difference in regions of the gland. Apart from the different types of neoplasms occurring in these regions of the gland, physiologic proof has been difficult to obtain concerning the duality of the human prostate. Subtle but definite effects are observed after estrogen administration which I shall present in a moment revealing regional differences in the human prostate.

Aside from the differentiation of the prostate into cortical (posterior lobe) and medullary portions (inner prostate, periurethral region), the prostate does not seem to have other lobes. At the present time a "median lobe" is commonly described but the terminology is inexact. Our observations coincide with those of Swyer¹⁸ who states—"In most cases the fibroadenomatous nodules of early prostatic hypertrophy are found only in the lower parts of the prostate, and it is by the upward extension of these nodules that intravesical projections are generally formed. Rarely the projections take the form of a more or less complete collar around the internal urethral meatus, but it is much more common to find a median knob, often referred to as the uvula vesicae, behind the meatus. Very occasionally, a uvula vesicae may exist without there being any evidence of hyperplasia in the lower parts of the prostate; these are the cases of true subcervical or subtrigonal lobe hyperplasia." In most cases the median lobe or uvula can be traced to a lateral adenomatous nodule.

4. *The androgenic relationship.* Constantly in benign prostatic hypertrophy the prostatic epithelium consists of tall columnar cells 16-28 μ in height.¹⁹ In the dog and the rat castration causes a prompt decrease of height of the cell, which is restored by androgen. In man orchiectomy causes a decrease of cellular height and epithelial atrophy in the benign hypertrophy but at a rather slow rate compared to the laboratory animals. The epithelial cells were only slightly reduced 29 days after castration but marked atrophy was observed¹⁹ at eighty-six and ninety-one days.

Orchiectomy produced a considerable relief of obstructive symptoms and a decrease in the size of the prostatic hypertrophy in our cases. However enucleable spheroids of muscle, fibroblasts and atrophic epithelium were present so that the neoplasm did not disappear—it merely shrank in size. Of importance in the etiology of benign hyper-

trophy is the fact that it has never been observed in man from whom the testes had been removed in early life.

The effect of estrogen on the prostate requires special comment. In the dog estrogen results in a rapid cessation of secretion and profound epithelial atrophy with pronounced epithelial metaplasia of the posterior segment of the gland. In man the effect is much less and slower. Moore and McLellan²⁰ injected estrogen for ten to thirty-one days in five patients with benign prostatic hypertrophy and observed an increased stratification of the transitional epithelium in the ducts and urethra; the acini and stroma of the nodules of benign hypertrophy showed little effect of the estrogen. In our experience with man estrogen administered in dosage sufficient to cause breast growth (e.g. diethyl stilbestrol 130 mg. in fifty-seven days, of which 70 mg. were injected intramuscularly) caused no decrease in the amount of enzymic concentration of prostatic fluid; definite changes were observed in the acini of the inner prostate and none in the posterior lobe. In the acini of the medulla of the prostate a paleness of the cells, vacuolation and signs of mild injury such as a shift of the nucleus to the middle of the columnar cell were observed contrasted with the normal epithelial cells of the cortical prostate.

DISCUSSION

In the hyperplastic prostate of dogs the lesion is primarily a great epithelial growth conditioned by 2 factors, the testis and time. Fibromas and myomas have not been observed. The epithelium is inefficient since the prostatic secretion is much reduced in quantity though qualitatively similar to the secretion of a normal young adult.

Since hyperplastic epithelium is the basis of the canine overgrowths theory suggests that the epithelial cells are the basic factors in the human prostatic enlargement. In most cases in man the lesion is an adeno-fibro-myoma; in those cases of pure myoma or fibroma the earlier presence of epithelium which has been "choked off" cannot be excluded. The nodular character of the process and its respiration indicate that the disease is a benign neoplasm. Since the prostate has the peculiar property of continued growth the frequent presence of abnormal growth processes is not unexpected.

In man the disease involves only the medullary part of the prostate. Comparative physiology has shown that there are 2 functionally dif-

ferent areas of the prostate in mouse, guinea pig and monkey. The evidence that the human prostate is composed of 2 different regions, apart from the capacities of the posterior lobe and the medullary region to form differing neoplasms, is based on differences of embryologic origin and response to estrogen of these regions.

Certainly in both man and dog prostatic enlargement is related to a stimulus acting for a very long time since the disease does not occur in early life. Presumably the stimulus is of testicular origin since the disease does not occur in the absence of the gonad. Obviously androgen is a basic factor in development if not the actual cause since tall epithelium is invariably present in the gland in prostatic hypertrophy, and the disease does not occur in feminized dogs. Also castration causes shrinkage²¹ of this neoplasm which has never been known to develop in castrates. Finally androgen itself is a powerful stimulant of growth of selected cell areas.

It must be pointed out at this time that while estrogen is involved in the genesis of many tumors, androgen as yet has not been implicated as an inciting agent for tumors in any experiment.²²

It is proven that androgen is a basic element in the etiology of benign prostatic hypertrophy. However in man in old age at a time when prostatic tumors are growing well there is a decreased secretion of androgen. Rusch and Kundert²³ first showed that the androgen excretion of men with prostatic hypertrophy is significantly lower than that of young males. Dingemanse and Laqueur²⁴ observed that both the urinary estrogens and androgens were less in men with benign prostatic hypertrophy than in old men without this lesion. The reduction in the amount of urinary androgens in old age has been confirmed by other groups^{25,26,27} using both the comb growth assay technique and the Zimmermann reaction for 17-ketosteroids. Teem⁶ found that the number of Leydig cells in the testis of men with benign prostatic hypertrophy is relatively reduced.

Growth of the prostatic hypertrophy in the face of greatly reduced androgen is well explained by the endocrinologic doctrine of threshold. The prostate has a lower threshold to androgen than the seminal vesicle. Working with crude extracts Moore and Gallagher²⁸ found that about 3 times as much androgen was required to show effects in the seminal vesicle as in the prostate. This has been confirmed with pure androgens.^{29,30} There is a differential threshold in the prostatic lobes in the

rat to androgen. On the tenth day after castration involutionary changes were first detected cytologically in the anterior lobe (coagulating gland) although they had been noticed on the fifth day in the other prostatic lobes.³⁰ The evidence that there is a low threshold to androgen in human prostatic hypertrophy is based on the slowness of development of post-castrational atrophy and the resistance to estrogen in comparison to the laboratory animals.

CONCLUSION

The epithelium of the cortical prostate differs from that of the benign prostatic hypertrophy in its response to estrogen; this observation indicates that the prostate gland of man is composed of two different functional areas.

Benign prostatic hypertrophy in man consists of multiple spheroidal neoplastic nodules arising in the medullary portion of the prostate because of a testicular stimulus presumably androgen acting over a long period of years on a tissue which at that time has a low threshold to androgens.

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DIAGNOSIS OF THE TETRALOGY OF FALLOT AND MEDICAL ASPECTS OF THE SURGICAL TREATMENT*

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THE tetralogy of Fallot, as described by Fallot,¹ consists of pulmonary stenosis or atresia combined with dextro-position of the aorta, an interventricular septal defect, and right ventricular hypertrophy. It is worthy of note that although Fallot emphasized that such cases constituted a pathological entity, the first case was described more than 100 years earlier by Sandifort.²

The pulmonary stenosis usually involves the musculature of the right ventricle below the pulmonary valve. Sometimes the stenosis extends up to the valve itself as in Figure 1. It is, however, common to find the maximum stenosis occurs in the infundibulum of the right ventricle as shown in Figure 2. Although the pulmonary artery is usually smaller than the aorta, the pulmonary artery beyond the pulmonary valve is normally formed. Dextroposition of the aorta means that the aorta, although it arises from the left ventricle, over-rides the top of the ventricular septum and receives some blood directly from the right ventricle. The over-riding of the aorta renders inevitable a high ventricular septal defect. Such is the nature of the "interventricular" septal defect in the tetralogy of Fallot. The pulmonary stenosis and the dextroposition of the aorta both increase the work of the right ventricle. Consequently there is right ventricular hypertrophy.

Clinically a patient with this malformation shows cyanosis and clubbing and a heart of normal size. A systolic thrill and a harsh systolic murmur along the left sternal border are of common occurrence, but neither the murmur nor the thrill are essential for the diagnosis. Indeed if the pulmonary stenosis is extreme too little blood may pass through the pulmonary orifice to produce a murmur. The over-riding of the

* From the Department of Pediatrics of the Johns Hopkins Medical School and the Harriet Lane Home of the Johns Hopkins Hospital, June 1947.

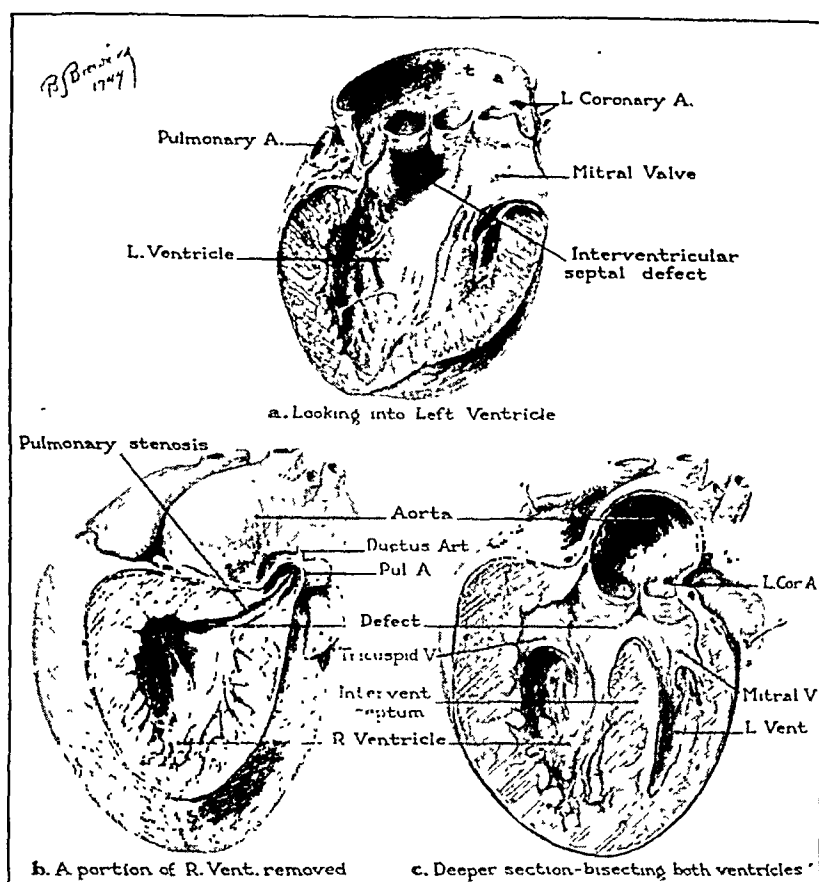


Figure 1: Tetralogy of Fallot.

aorta in a tetralogy of Fallot does not in itself cause a murmur.* The intensity of the second sound varies with the size and position of the aorta. It may be louder to the left than to the right of the sternum. Nevertheless, inasmuch as there is pulmonary stenosis, the second sound at the base is never reduplicated. Indeed the only significant auscultatory finding is the purity of the second sound at the base of the heart.

The blood pressure is narrow and often difficult to obtain.

The electrocardiogram shows a right axis deviation. Almost always the P waves in Lead II are abnormally high; frequently they are 5 mm. in height and occasionally 10 mm.

The diagnosis is established by fluoroscopy. Although in some instances the heart is slightly enlarged, it is usually within normal

* This statement is based upon clinical findings which have been repeatedly checked at autopsy.

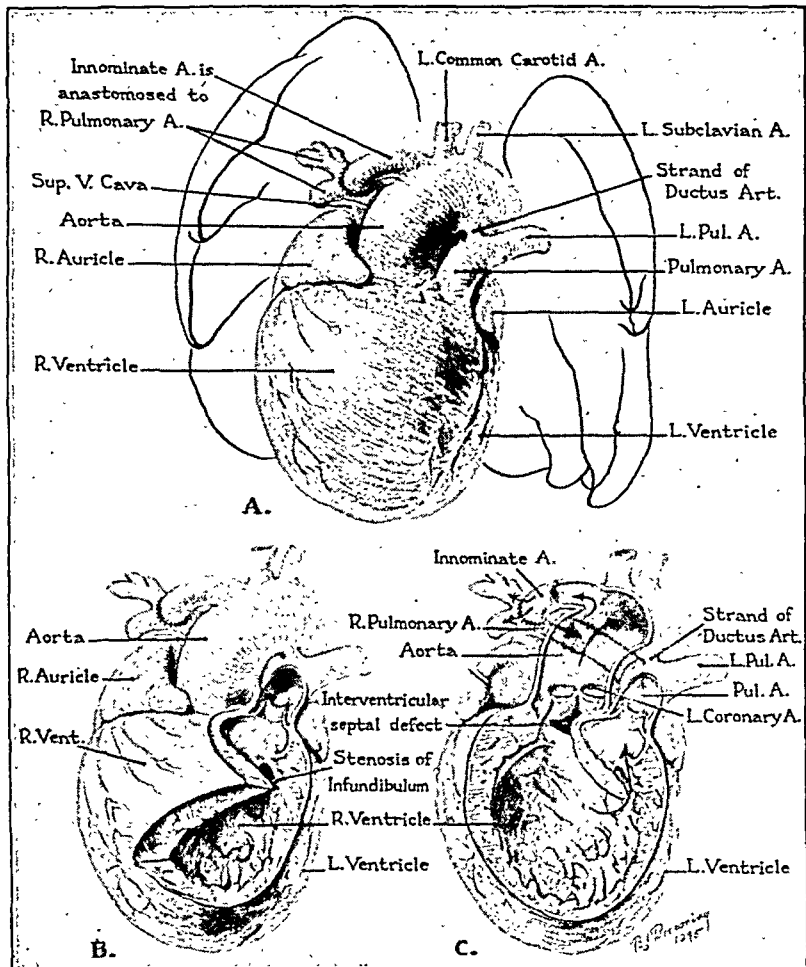


Figure 2: Tetralogy of Fallot, showing Infundibulum Stenosis and Anastomosis of Innominate Artery to Right Pulmonary Artery.

limits. The contour of the heart is characteristic. There is no fullness in the region of the pulmonary conus; consequently the shadow at the base of the heart to the left of the sternum has a concave margin (see Figure 3). Examination in the oblique views is of diagnostic help. In the left anterior oblique position, the heart is but slightly enlarged and the pulmonary window (i. e., the area below the aortic window which is usually occupied by the pulmonary artery) is abnormally clear. In the right anterior oblique position, the upper margin of the cardiac silhouette shows a concavity at the junction of the aorta with the right ventricle.

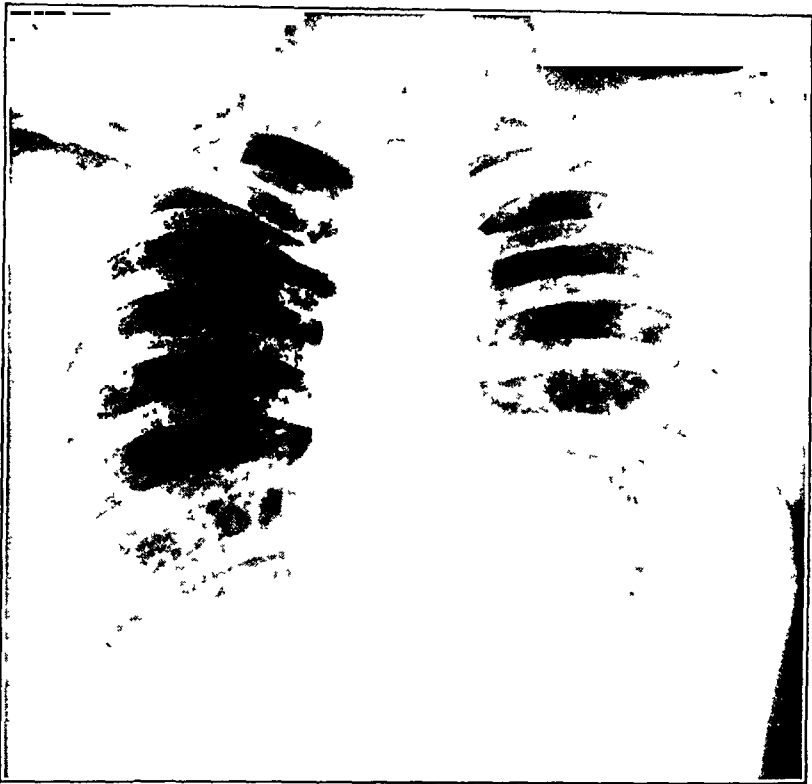


Figure 3: Tetralogy of Fallot with Left Aortic Arch.

The hilar shadows are of prime importance. Owing to the diminished pulmonary blood flow, the hilar shadows are usually minimal. Occasionally, if the principle pathway of the collateral circulation is by way of the posterior mediastinal arteries these shadows become dense.

The contour of the heart characteristic of a tetralogy of Fallot is easily differentiated from that in which there is fullness of the pulmonary conus (see Figure 4). Such a contour is indicative of a large normally placed pulmonary artery and usually connotes excessive circulation to the lungs. Not infrequently upon fluoroscopy a hilar dance is visible. Dancing hilar shadows are caused by pulsations in the pulmonary vessels and are indicative of excessive pulmonary blood flow to the lungs. Hence such shadows are a contraindication for operation.

The x-ray contour shown in Figure 5 is less readily differentiated from that of a tetralogy of Fallot. However, upon fluoroscopy after the observer's eyes were fully accommodated, there were expansile



Figure 4: Eisenmenger Complex.

pulsations in both hilar regions. In such cases, even though the patient is cyanotic, operation is contraindicated.

Although not essential for the diagnosis of a tetralogy of Fallot, prior to operation it is important to ascertain the direction of the aortic arch. A right aortic arch occurs in 20 to 25 per cent of all cases of a tetralogy of Fallot. Under such circumstances, the innominate artery lies to the left of the sternum. Furthermore, the subclavian artery is given off the innominate artery at a better angle for anastomosis than it is from the arch of the aorta. Therefore the operation is best performed on the opposite side to that upon which the aorta arches.

The position of the aortic arch is determined by x-ray and fluoroscopy.³ With a normal left aortic arch, the aortic knob is usually visible upon the left. Upon the delineation of the esophagus with a barium



Figure 5: Heart with a Contour similar to Tetralogy of Fallot, but with Pulsations in the Hilal Regions.

opaque mixture, the esophagus descends in the mid-line and is indented by the aorta on its left margin to the right. Examination in the oblique positions aids in determining the course of the aorta. In the right anterior oblique position, the esophagus hugs the cardiac shadow and is slightly displaced posteriorly by the arch of the aorta; in the left anterior oblique position, the esophagus descends independently from the aorta. When the aorta arches to the right and descends upon the right, the aortic knob lies within the shadow cast by the superior vena cava; consequently in the A-P position the aortic knob is seldom visible. The esophagus is deviated to the left. It usually lies at the extreme left margin of the great vessels and its right border is indented to the left by the aorta (see Figure 6). If the esophagus is displaced backward by



Figure 6: Tetralogy of Fallot with a Right Aortic Arch (A.P. View).



Figure 7: Tetralogy of Fallot with Right Aortic Arch (Right-Anterior Oblique View).

the aorta the displacement is visible in the left anterior oblique position. Even if this does not occur, the esophagus in the right anterior oblique position descends independently from the heart and the aorta (see Figure 7).

The operation is designed to increase the circulation to the lungs by the creation of an artificial ductus arteriosus.^{4,5} This is accomplished by the anastomosis of the proximal end of either the subclavian artery, the innominate artery, or the common carotid artery to the side of the right or left main pulmonary artery. Such an operation is described as an end-to-side anastomosis. Collateral circulation is relied upon to carry the blood to the part which has been deprived of its normal circulation. In our experience the collateral circulation to the arm is always adequate: no difficulty has resulted from the sacrifice of the subclavian artery.* When the innominate or the common carotid artery is used there is danger of cerebral thrombosis. Usually, however, this can be overcome. Whenever possible it is preferable to use the subclavian artery. Occasionally the right pulmonary artery is abnormally short and consequently it is necessary to sever the pulmonary artery and to anastomose the proximal end of the systemic artery to the distal end of the right pulmonary artery. Such an operation is spoken of as an end-to-end anastomosis.

Although an end-to-end anastomosis is technically easier than is an end-to-side anastomosis, wherever possible an end-to-side anastomosis is preferable. An end-to-side anastomosis permits the flow of blood to both lungs whereas an end-to-end anastomosis places the entire load upon one lung. Furthermore, with an end-to-side technique the two vessels used for the anastomosis do not need to be of the same size. If the end of a large vessel is anastomosed to the end of a small vessel, thrombosis is liable to occur at the site of the anastomosis. The end-to-side anastomosis has the additional advantage that if the vessel is not sufficiently large or does not increase in size with the growth of the child, it should be possible, at a future date, to perform a similar operation on the opposite side. Finally, if thrombosis occurs following an end-to-side anastomosis, the resulting condition is the same as it was prior to operation whereas in case of thrombosis of an end-to-end

* The author has heard of one case in which the arm was injured by the sacrifice of the subclavian. In that case the child had a hemiatrophy and the radial pulse was not palpable before operation. At operation the subclavian artery was of good size. Evidently if a good-sized subclavian artery does not give a pulse at the wrist, collateral circulation is not sufficient to compensate for the sacrifice of this vessel.

anastomosis, the circulation to the entire lung is cut off; this is almost inevitably fatal.

The indications for operation vary with the age of the patient and depend upon the severity of the pulmonary stenosis and upon the height of the compensatory polycythemia. Children are a better operative risk than are infants or adults. Therefore, whenever possible it is advisable to postpone operation until the patient is over two years of age and to perform it before he is fifteen years of age.

Early operation is indicated if an infant suffers from repeated attacks of paroxysmal dyspnea or the anoxemia is of such severity as to cause loss of consciousness. If, however, the general condition of the infant is good and the attacks are not severe, it is wiser to postpone operation until the child is older. Delay in sitting, crawling, or walking is not sufficient indication for operation under two years of age.

In children and young adults the indications for operation depend mainly upon the degree of incapacity of the individual and the height of the red blood cell count and the hematocrit reading. A person with an extreme degree of polycythemia, as for example, a red blood cell count of 8.5 million or above, or a hematocrit reading of over 80, is in danger of cerebral thrombosis. Successful operation causes the red blood cell count, the level of the hemoglobin, and the hematocrit reading to return to normal and thus eliminates this danger. Children who are markedly incapacitated, even though they do not have a polycythemia, can be greatly benefited by operation. Such children have a very low oxygen saturation of the arterial blood or the oxygen saturation of the arterial blood drops markedly with exercise. A child with an arterial oxygen saturation of 30 per cent usually can walk only a few feet. If the oxygen saturation of the arterial blood drops markedly with exercise it is a definite indication for operation. In one instance, that of a four year old boy, the oxygen saturation of the arterial blood dropped from 41.2 to 15.2 per cent upon climbing two steps, three times. Indeed if the oxygen saturation drops from 80 to 50 per cent on exertion, that, too, is an indication for operation.

If there is evidence that, in the future, operation will be necessary, it is advisable, whenever possible, to operate before 12 or 14 years of age. The tissues of an adult are less resilient than those of a child and the lungs do not adjust as readily to the increased circulation.

The choice of the vessel to be used at operation depends upon the

size of the vessels and the severity of the reduction of the pulmonary blood flow. In infants the subclavian artery is a tiny vessel; therefore the use of the innominate artery is almost invariably indicated. On the other hand, in patients over fourteen years of age the use of the innominate artery is almost always contraindicated; it places too great a strain upon the lungs. Therefore it is only in children that the selection of the vessel is of concern. Whenever possible the use of the subclavian artery is preferable to the innominate artery because as previously mentioned, the former entails less danger of cerebral thrombosis. Recent experience has shown that in children over two years of age, the subclavian artery is usually sufficiently large to raise the oxygen saturation of the arterial blood to 70 or 80 per cent. If the child is of frail build the subclavian may be a small vessel. It is advisable under such circumstances to postpone the operation, if possible, until the child is six or seven years of age in order that the subclavian artery will be sufficiently large to give the desired increase in the pulmonary circulation.

The benefit derived from increasing the circulation to the lungs is immediately apparent. When the patient is first anesthetized and given a high concentration of oxygen, his color improves greatly. After the opening of the chest and the collapse of one lung, he becomes cyanotic. When the circulation to that lung is cut off, the child usually becomes deeply cyanotic. This is of no great concern provided the heart action remains strong. After the completion of the anastomosis, just as soon as the clamps are removed and blood flows to the lungs, one can watch the patient's color improve. As the lungs are re-expanded the color continues to improve. By the time the chest is closed and the drapes are removed and oxygen has been discontinued, the patient's lips are usually of normal color. Indeed, the color of the patient's lips and cheeks at this time generally gives an indication of the amount of benefit derived from the operation. Although the maximum arterial oxygen saturation is not immediately obtained there is an abrupt increase in the oxygen saturation of the arterial blood at the end of operation. In one case it rose from 30 to 69 per cent; in another from 24 to 63 per cent.

If the polycythemia is marked or if the cerebral circulation has been disturbed, venisection at the end of operation is a sound physiological procedure. Just as soon as the circulation to the lungs is increased, the need for the polycythemia has been removed. Venisection at this time lessens the load upon the lungs and lessens the danger of cerebral throm-

bosis. A normal adult can give 500 cc. of blood without difficulty. A child with a marked polycythemia is greatly benefited by the withdrawal of 100 to 250 cc. of blood depending upon the size of the child and the degree of the polycythemia.

The routine postoperative care includes the use of oxygen, penicillin, sedation and the careful regulation of the fluid intake. The last mentioned is the only one of these procedures which requires special consideration. The maintenance of correct fluid intake before, during and after operation is of great importance.

Inasmuch as patients with polycythemia are liable to develop cerebral thrombosis it is always important to prevent dehydration. Prior to operation these children should always receive 1500 cc of fluid per day and young adults over 2000 cc. Care should be taken not to dehydrate the patient the night before operation. Twelve hours without fluid is liable to cause cerebral thrombosis even though the circulation to the brain is not disturbed. If the innominate artery or carotid artery is used at operation, the danger of cerebral thrombosis is increased.

There is, however, less danger of postoperative pulmonary edema and pulmonary effusion if a low fluid intake is maintained during and immediately after operation. During the operation the patient is given slow continuous intravenous fluid so that in case of hemorrhage the blood loss can be promptly replaced by plasma. Except in cases of hemorrhage, the infusion of plasma should be small in order to lessen the danger of pulmonary edema upon the release of the clamps after the completion of the anastomosis. During the first twenty-four hours (midnight to midnight) of the day of operation, most infants require 750 to 900 cc. of fluid; children two to ten years of age require approximately 1000 cc. of fluid and adults should not receive over 1800 to 2000 cc. of fluid. This total fluid intake includes the fluids given during the operation (except that which is required to replace blood loss from severe hemorrhage): the fluids given intravenously, and that which is taken by mouth. Therefore, if shortly after operation fluids by mouth are well tolerated, the intravenous fluid should be decreased or discontinued.

The most serious postoperative complications are cerebral thrombosis, pleural effusion, pneumothorax, cardiac failure and suppression of renal function and thrombosis at the site of the anastomosis. The last mentioned nullifies the benefit to be derived from operation.

Cerebral thrombosis and *hemiplegia* are especially likely to occur when the circulation to the brain has been disturbed by the use of the innominate or the common carotid artery. The danger is increased by the marked polycythemia and by dehydration. The period of greatest danger is four to twenty hours after operation. The development of a hemiplegia or of paresis of any of the extremities calls for prompt treatment. Heparin causes an immediate prolongation of the clotting time and therefore is of far greater benefit than is dicoumarol. The initial dose of heparin (0.5 mgm. per kilogram of body weight) is given intravenously; this is followed by the slow continuous administration of heparin. This is best accomplished by the addition of heparin to the plasma, glucose, or saline, which is given by continuous intravenous drip. The objective is to prolong the clotting time of the blood to twenty minutes. Approximately the same amount of heparin per hour is required to maintain the increased clotting time as is initially required to raise it to a given level. The estimated amount of heparin should be combined with the amount of fluid required per hour. For example, if the patient weighs 20 kilograms and is to receive 100 cc. of fluid per hour for the next few hours, 10 mgm. of heparin is added to 100 cc. of the fluid and the clotting time is checked at the end of one half hour. Then if the fluid is to be reduced to 75 cc. of fluid the next hour, 10 mgm. of heparin should be added with the next 75 cc. of fluid provided the desired clotting time is obtained. If the clotting time is not sufficiently prolonged, more heparin is added to the solution; if it is excessively high, more fluid is added and the concentration of the heparin is thereby reduced. It is advisable to continue to use heparin for 12 to 48 hours depending upon the condition of the patient. If treatment is promptly instituted it is often possible to overcome the paralysis and prevent the development of any residual hemiplegia.

Pneumothorax may result from injury to the lung at the time of operation or from the use of too great positive pressure at the time of the re-expansion of the lung. The latter may occur on the side opposite to that of operation. Unless there is a tension pneumothorax, simple aspiration usually suffices. A tension pneumothorax may require continuous suction.

Pleural effusion is a common complication. The fluid is usually hemorrhagic. Pleural effusion occurs so frequently that a portable x-ray plate the evening after operation is a wise precaution. If there is no

demonstrable fluid eight to ten hours after operation, it is reasonably certain that there will be no serious embarrassment from a pleural effusion before morning; it does not however mean that no fluid will accumulate. Indeed, aspiration of a pleural effusion is often necessary one to two days after operation. Not infrequently repeated aspirations are needed. While there is any tendency for fluids to accumulate in the chest, care should be taken that the patient does not receive an excessive amount of fluid by mouth.

Slight increase in the size of the heart after operation is relatively common. Usually, however, once the heart has adjusted to the load placed on it by the altered circulation, there is no further cardiac enlargement. Slight engorgement of the liver frequently occurs during the first week after operation. Digitalis is helpful at this stage, but if the child responds promptly, it is seldom necessary to continue it over a period of weeks. Diuretics, especially theocalcin, are of value in cases of engorgement of the liver and are strongly indicated if the urinary output is low.

Suppression of kidney function is a common complication. The cause is not clear. Diuretic and digitalis are both helpful.

Hypertension in the early postoperative period is of frequent occurrence. It usually causes no concern; on the contrary, it improves the circulation to the brain and lessens the danger of cerebral thrombosis. It is important to remember that even though the blood pressure may be difficult to obtain before operation, it should be readily obtainable within two to three hours after operation. If the blood pressure does not rise promptly, plasma should be given or the rate of the flow of plasma should be increased.

Although there are many possible serious complications, it is remarkable how smooth the postoperative course usually is and how rapid and how great is the improvement. A liquid diet may be allowed on the day of operation and the following day a soft diet is often desired. The child is usually free of pain and comfortable without oxygen in four days time and ready for discharge in two to three weeks.

The results of the first three hundred operations are briefly summarized as follows: 54 (18 per cent) have died at, or shortly after, operation; 9 cases (3 per cent) were found to be inoperable but survived an exploratory thoractomy. Ten children (3.5 per cent) were unimproved by operation; in most of these cases thrombosis occurred

at the site of the anastomosis. Three of the patients who were unimproved, died within six months of operation. Eleven or 4.5 per cent were helped but not brilliantly improved. Two hundred and fifteen patients (71 per cent) were greatly benefited by operation. An excellent result means that the cyanosis virtually disappears; that the lips are of normal color, there may be slight cyanosis of finger tips but clubbing recedes. The oxygen saturation of the arterial blood rises to 80 per cent or above and the red blood cell count, the hemoglobin level, and hematocrit reading return to normal values. The heart, is, of course, not normal. On the contrary, murmurs are louder than before operation; and in addition to the systolic murmur, there is a loud continuous murmur heard throughout the chest, front and back. The amount of increase in the heart size has varied considerably but after the initial increase, in only one instance during the first postoperative year, has there been evidence of progressive cardiac enlargement.

Although the heart is not normal and the danger of subacute bacterial endocarditis is not eliminated, both the danger of dying from anoxemia and the danger of cerebral thrombosis have been overcome. The child is able to measure his exercise tolerance not in terms of feet but in terms of miles. Although it is too early to determine whether the child's life may or may not be prolonged by operation, it is certainly happier.

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